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Editorial

Myocarditis

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Not long ago, Thomas Lewis stated that the use of the term "myocarditis" is scarcely justified clinically except in respect to rheumatism. He said that in this relation the term "carditis" is sounder. He thought that the description of myocarditis as a separate disease with its special symptoms and signs needlessly complicates the general description of cardiac disease, which should remain simple. In a rather philosophic vein, Rothschild, in a volume in honor of Dr. Emanuel Libman, discussed disturbances of function of the heart which seemingly occur without demonstrable morphologic changes. He ventured that the incapability of the pathologist to find anatomic changes (myocarditis) forced clinicians to become more discerning; they then began to analyze more closely just what part of the entire circulatory mechanism was at fault. Because of this attitude, he said, the diagnosis of myocarditis became less frequent and, "prophetically will become even less frequent." H. A. Christian stated, "If by acute myocarditis is meant an actual inflammatory process of the myocardium with infiltration by polymorphonuclear leukocytes, this is a rare condition and consequently of minor clinical importance. On the other hand, if by acute myocarditis is meant the circulatory disturbances, with or without evidence of degeneration of the muscle fibers or cellular infiltration between them, associated with acute infectious diseases, it is a frequent occurrence." It seems that because of the skepticism of leading clinicians, and because of the inability of the pathologist (who examined microscopically only one or two sections cut from the myocardium) to correlate the clinical picture with the anatomic findings in those rare cases in which the clinician had made the diagnosis of myocarditis, both the clinician and the pathologist lost interest in this lesion. It was apparently for this reason that Edens, in a monograph on diseases of the heart and blood vessels, called myocarditis the "stepchild of Pathology." The blame did not

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solely rest with the clinician. "Chronic myocarditis" had fallen into disrepute because it had been applied, incorrectly, of course, to myocardial changes, the result of coronary artery disease. If, in spite of this knowledge, the astute clinician occasionally diagnosed myocarditis in a young patient, he often was not supported by the pathologist at the autopsy table. Myocarditis is a difficult diagnosis to arrive at on gross inspection. If only a few sections cut at random from the myocardium are examined, the pathologist is bound to fail to make the diagnosis. It was often the pathologist's fault for not having examined the heart thoroughly which discouraged the clinician from making the diagnosis in some cases. This state of affairs obviously had led to Lewis' and Rothschild's stand.

Whatever it might be, the clinician often avoided the diagnosis of myocarditis. It was often remarkable how rarely myocarditis was diagnosed as a special entity, and this is still true to a certain extent. One often may observe in clinico-pathologic conferences to what subterfuges the clinician will resort rather than diagnose myocarditis in discussing a young patient with perhaps fleeting electrocardiographic changes, abnormal rhythms, S-T and T-wave changes, etc., dying in acute cardiac failure. It was due to the combined efforts of the pathologist who began to examine the myocardium histologically with the utmost care, and the young clinician who with stubborn effort insisted that inflammatory changes in the heart should be present, that myocarditis today is not only an accepted disease, but is regarded as not rare, frequently complicating existing diseases and sometimes also constituting the primary disease and cause of death.

While it is often assumed that morphologic methods are antiquated and that no new facts are forthcoming, the evaluation of the concept of myocarditis and its clinical acceptance during the last few years bear witness that painstaking morphologic studies still have a place in modern medicine. During the last decade a number of well-documented clinical and anatomic studies have appeared in the medical literature. Reports of groups of cases are increasing every year and, contrary to Rothschild's "prophetical" view, myocarditis will be recognized still more often if the clinician and the pathologist further concentrate their efforts.

In spite of the fact that myocarditis is now recognized clinically much more often than a few years ago, there are still a number of patients dying from undiagnosed myocarditis. While the autopsy incidence of myocarditis is usually given as about 3.5 per cent of all cases, and while this incidence rises to about 8 to 10 per cent if many sections are cut from the myocardium, myocarditis is still diagnosed clinically in only about a half to one fourth of the cases.

Early investigators were concerned principally with myocarditides occurring in rheumatic fever and in the various endocarditides. Also, myocarditis occurring in the wake of bacterial and parasitic diseases was studied and its importance acknowledged. Among this type of infectious diseases, it was principally diphtheritic myocarditis upon which attention was focused. Even now, reports of myocarditis, sometimes with permanent myocardial damage, appear in the literature in spite of some claims that diphtheria is practically eradicated. The role of syphilis as an etiological agent of diffuse myocarditis

was disputed over a number of years. While syphilis was considered of paramount importance some time ago, it is generally believed today to play only a minor role—if existing at all. Myocardial changes in syphilis do occur, of course, but they are the result of concomitant changes at the mouth of the coronary arteries or perhaps of complicating diseases.

Fungus myocarditis is more common now than ever before, in some instances clearly related to antibiotic treatment. Thus, reports of *Candida albicans* and *Aspergillus* myocarditis, etc., have appeared in the more recent literature. In my own experience, these fungus myocarditides may be very severe and destroy much of the myocardium. Among protozoal disease, myocardial toxoplasmosis is more frequently recognized. Amebic involvement of the myocardium still is very rare. Chagas' disease as a cause of chronic myocarditis has assumed a very important role in South America. Myocardial fibrosis, in many instances still accompanied by a few inflammatory cells, has been traced to past infections with the leishmanian form of the *Trypanosoma cruzi*.

Fiedler's, or isolated, myocarditis has continued to hold the interest of investigators, with occasional case reports over the years since first reported in 1899. It may appear in an acute or chronic form, sometimes simulating myocardial infarction with precordial pain, in a relatively young individual, or may manifest itself as a protracted myocardial disease with a continuously progressing downhill course. Very rare too, but with occasional cases being reported, is a granulomatous, or giant cell myocarditis, which either resembles Fiedler's myocarditis clinically or causes unexpected sudden death with practically no clinical symptoms.

Myocarditis associated with hypersensitivity has been known for many years to occur following the administration of arsphenamine, sparteine, bismuth, etc., but has received more widespread attention since its occurrence in patients treated with sulfa preparations. So-called hyperergic granulomas, eosinophils, and, sometimes, periarteritic changes are significant. Noteworthy in this respect is the increase of reports of myocarditides in the wake of modern therapeutic measures. Thus, myocarditis has been described recently as a result of treatment with l-norepinephrine (Levophed). This brings to mind previously published electrocardiographic changes in instances of pheochromocytomas.

More and more attention is being given to myocarditis in the various virus diseases. It is evident that myocarditis is a rather common complication. In spite of the fact that a virus has been actually demonstrated in the myocardium in only a very few instances, it does seem clear, because of microscopic similarities, that the myocarditis is caused by the virus. Myocarditis has been observed in cases of mumps, chickenpox, smallpox, and also following vaccination against these diseases, in viral pneumonia, in various influenzal virus diseases, in infectious mononucleosis, in viral hepatitis, in poliomyelitis, in certain encephalitides, and in infections with encephalomyocarditis (EMC) virus. The latter virus, originally discovered in a gibbon, has been found sometimes in human beings and especially in children. It is interesting in this respect that there are a number of reasons for predicting that cases of EMC virus infection in childhood may be found more frequently in this country if sufficiently sought for. The reasons

for this prediction are: (1) the presence of encephalomyocarditis antibodies in the sera of normal persons; (2) the knowledge that wild rats in the United States are probably harboring this virus; and (3) reports of isolation of the EMC virus from young children in Europe who have a variety of diseases of the central nervous system with lymphocytic pleocytosis in the cerebral spinal fluid.

Myocarditis resulting from the Coxsackie virus disease has been found in infants, apparently transmitted in utero. Small epidemics occurring in nurseries have been described. In poliomyelitis, myocarditis has been found in as many as 42.4 per cent of the cases. It has been claimed that abnormal electrocardiograms are rare in nonparalytic cases, that there is a 25 per cent incidence of electrocardiographic changes in spinal poliomyelitis with moderate paralysis, a 40 per cent incidence in cases with more severe paralysis, and a 50 per cent incidence in cases with bulbar paralysis.

The question is often raised of how sometimes only a few inflammatory cells in some foci, combined with a serous exudate, in a given section, can possibly be of clinical significance. It must be realized that routinely only a few sections, 5 to 12 micra thick, are examined, so that the sum total of myocardial mass examined constitutes only an infinitesimal portion of the myocardium. However, when only a few changes are recognized in a few sections taken at random, it stands to reason that similar changes are also present in other portions of the myocardium. Besides, a serous component of the exudate is often overlooked, but may be diffuse and of serious consequence in regard to myocardial function.

The importance of recognizing myocarditis lies, of course, in the awareness of the clinician that this condition exists and, in some cases, may be reversible, so that supportive measures may be taken. While there is no agreement as to the type of medication, because myocarditis may occur in the wake of a number of diseases, preventive means are perhaps the most important. There is no unanimity as to whether digitalis preparations are indicated. Cortisone, corticotropin, and antibiotics have been used. Complete bed rest is strongly indicated from a purely morphologic point of view and a realization of the temporary detriment which may be brought about by a serous component of the myocardial exudate, which, of course, is transient and may regress without leaving permanent damage. As in many fields, the therapy will be worked out when the recognition and understanding of the disease itself becomes accepted medical history.

Clinical Communications

Postpericardiotomy Syndrome in Congenital Heart Deformities

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Postcommissurotomy syndrome is a well-documented entity. The increase in surgical treatment of congenital heart deformities justifies re-emphasis of the fact that a similar syndrome occurs following pericardiotomy in patients without rheumatic heart disease. The major feature of the syndrome is a pericarditis characteristically following the opening of the pericardium, and sometimes associated with pleural effusion or pneumonia. Recognition of the syndrome is important, because the management differs from that of cases of postoperative infectious infiltrations of the lung and other courses of sudden cardiac enlargement. The patients evidencing this syndrome have been found in various age groups, have been hospitalized at several different institutions, and have been operated upon by various heart surgeons. The syndrome usually appears between one and two weeks postoperatively, but may, as in one case, take as long as two months to appear, and does not necessarily accompany any other postoperative complication.

In the past three years the number of congenital defects being surgically explored and corrected in various hospitals has increased markedly. It is not surprising, therefore, that the number of patients developing the postpericardiotomy syndrome has also increased. Milstein and Brock,[1] in 1955, were the first to describe the problem, and recently, Ito, Engle and Goldberg[2] reviewed 13 cases.

During a recent period of approximately three years, the author has encountered at least 11 patients illustrating varying degrees of severity of this clinical problem. These 11 patients are described, and the pertinent data associated with the diagnosis, treatment, and follow-up are reported. The author has obtained a history of similar occurrences in a number of other patients, but because adequate study has not been made or was not possible, these cases cannot be included in the present findings.

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The patients were approximately equally divided as to sex (Table I). The syndrome occurred most often in the age groups of 6 to 10 and 11 to 15 years; this finding is probably related to the greater number of patients being operated upon in these two age groups. The syndrome occurred in 3 cases of pulmonary stenosis, in 7 cases of atrial septal defect (2 of which were associated with transposed pulmonary veins and 1 with mitral insufficiency), and in 1 case of aortic stenosis. In the patients with pulmonary stenosis, 1 underwent transcardiac surgery and 2 underwent a supracardiac valvulotomy; atrial defects were closed by the open technique, except as noted. Hypothermia was used in all except one of the patients undergoing supracardiac valvulotomy and in the patient undergoing transcardiac valvulotomy (Table II). Symptoms usually occurred either in less than seven days or between fifteen and thirty days (Table III).

TABLE I. VITAL DATA

Sex:	Males 5	
	Females 6	
Age:	Under 5 yr.	1
	5-10 yr.	4
	11-15 yr.	4
	16-20 yr.	1
	Over 20 yr.	1

TABLE II. CLINICAL DATA

DIAGNOSIS	SEVERITY			NUMBER OF PATIENTS UNDERGOING HYPOTHERMIA	TYPE OF SURGERY	
	MILD	MODERATE	SEVERE			
Pulmonary stenosis (3)		2	1	1	Supracardiac valvulotomy Transcardiac	2 1
Atrial septal defect (7)	1	3	3	7	Auriculotomy with closure Closed method	6 1
Aortic stenosis (1)			1	1	Supracardiac valvulotomy	1

Evaluating symptoms in children, especially those with cardiac problems, cannot always result in precise observations. Several factors must be taken into account, such as age, realization that these symptoms may occur, the factor of threshold to pain, parental overindulgence (which is frequently seen in cases of congenital heart problems), and severity of the lesion. Fever was seen as the primary symptom in all cases. Generalized chest pain was observed in 3 patients, and specific pain in the area of the sternum in 2 others. Pain in the left shoulder and arm was seen in 3 patients, and apprehension, appearing after several days of well-being, was noted in 4 (Table IV). Four patients developed poor heart tones consistent with pericardial fluid. A friction rub was heard in 6. Decreased

breath sounds and dullness of the chest consistent with pleural effusion, either unilaterally or bilaterally or changing from one side to the other, was observed in 6. A tender and/or an enlarged liver was observed in 6 patients (Table V).

Six of the patients developed anemia after a period of stability in the postoperative time; in 4 of these the hemoglobin level was under 10 grams. Five had a white blood cell count of 10,000 to 15,000, and in three it was over 15,000. Electrocardiograms registered low voltage of the QRS in 3 patients, and T-wave or S-T abnormalities in 10 patients. X-ray findings showed a characteristic enlargement of the heart either at the time of development of the aforementioned symptoms and signs or within one to two days thereafter. Decreased pulsations of the heart on fluoroscopy were observed in 2 of the patients, pleural effusion was noted in 7, and pneumonia or pneumonitis in 5 (Table VI).

All of the patients were placed on a decrease in activity or complete bed rest during a portion of their acute phase. Three received antibiotics, and apparently showed no shortening of their recovery period over those not receiving antibiotics.

TABLE III. NUMBER OF POSTOPERATIVE DAYS BEFORE ONSET

NUMBER OF DAYS	NUMBER OF PATIENTS
Less than 7	5
7–14	1
15–30	4
Over 30	1

TABLE IV. SYMPTOMS AT ONSET

SYMPTOMS	NUMBER OF PATIENTS
Fever	11
Chest pain (generalized)	3
Pain in area of sternum	2
Abdominal pain	2
Pain in left shoulder and arm	3
Apprehension	4
Vomiting	2

TABLE V. PHYSICAL FINDINGS AT ONSET

PHYSICAL FINDINGS	NUMBER OF PATIENTS
Poor heart tones	4
Friction rub	6
Decreased breath sounds and dullness of chest	6
Tender and/or enlarged liver	6
Dyspnea	1
Gallop	1
Tachycardia	2
Paleness	3

A pericardial tap was done on 2 patients, and in both instances a serosanguinous fluid was obtained. Because of the anemia, 2 of the patients required transfusions, and 2 required oxygen. One who developed auricular fibrillation required quinidine for conversion. Seven patients were placed on digitalis, because of enlargement of the liver, difficulty in breathing, increased pulsations in the neck, and other signs associated with severe pericarditis and heart failure; consequently, there was considerable subjective and some objective improvement (Table VII).

Fever subsided in 7 patients within two weeks, and after one month in 4 others. Chest pain ceased within two weeks in 1 patient and after one month in

TABLE VI. LABORATORY DATA

Hemoglobin Level:		ECG	
Less than 10 Gm.	4	Low voltage QRS	3
10-12 Gm.	2	Flattening of S-T and T waves	4
Over 12 Gm.	3	Depression or elevation of S-T segment	6
		Bradycardia	1
Elevated WBC		Auricular fibrillation	1
10,000–15,000	5		
Over 15,000	3		

X-Ray Findings:	
Generalized enlargement of the heart shadow	11
Decreased pulsations of the heart on fluoroscopy	2
Pleural effusion	7
Pneumonia or pneumonitis	5

TABLE VII. TREATMENT

TREATMENT	NUMBER OF PATIENTS
Digitalis	7
Pericardial tap	2
Transfusion	2
Antibiotics	3
Bed rest	11

TABLE VIII. DISAPPEARANCE OR MARKED DECREASE IN PRINCIPAL FINDINGS

FINDINGS	DURATION		
	2 WEEKS	1 MONTH	2 MONTHS OR OVER
Fever	7	4	–
Chest pain	1	4	–
Friction rub	5	1	–
Pleural fluid or pneumonia	5	2	–
Cardiac enlargement	2	4	4

the other 4. Friction rub disappeared in 5 of the patients after two weeks and in 1 after one month. Symptoms of pleural fluid and pneumonia disappeared within two weeks in 5 of the patients and after one month in 2 others. Cardiac enlargement as determined by x-ray decreased within two weeks in 2 of the patients, and after one month in 4, but persisted for over two months in 4 others. Auricular fibrillation developed in one patient at about the time that most of the pericardial and pulmonary findings disappeared. Subsequent to the clearing up of this condition, a lung infarction was noted, after which fever again returned and was followed, in turn, by a sequence of symptoms and findings suggestive of subacute bacterial endocarditis which required six weeks to two months for treatment. This child was not discharged from the hospital until five months after operation (Table VIII).

CASE REPORTS

Case 1 (*Fig. 1*).—C. S. was a 25-year-old white married woman with congenital valvular pulmonic stenosis. Her preoperative condition was considered to be poor and the stenosis severe. The pressure in the right ventricle was over 157 mm.Hg, frequent extrasystoles were noted, and she was described as being 3-plus to 4-plus cyanotic. At operation she would not tolerate hypothermia; therefore, a transventricular valvulotomy was carried out on Oct. 14, 1955. Her postoperative course was uncomplicated, and she was discharged on Oct. 26. At home she was permitted mild exercise. On October 31, fifteen days postoperatively she developed fever, loss of appetite, and pain principally in the sternal area. Physical findings revealed poor heart sounds, a friction rub, and frequent ventricular extrasystoles. An electrocardiogram revealed low voltage of the QRS complexes and flattening of the S-T and T waves in all leads. X-ray revealed tremendous enlargement of the cardiac shadow, and fluoroscopy showed reduced pulsations. She was immediately readmitted to the hospital and placed on complete bed rest, with no other treatment for one week. During her hospital stay the symptoms were pain, fever, and lethargy, and the physical findings were poor heart sounds, friction rub, and decreased breath sounds. She was seen again after discharge on November 12; there was some generalized improvement and decrease in the above-mentioned symptoms and signs. By December 10, the x-ray films showed almost complete clearing, and there were no further symptoms associated with the pericarditis. The tones of the heart were greatly improved, there were no further ventricular extrasystoles, and the breath sounds appeared to be within normal limits. On October 27, 1956, approximately one year following the aforementioned incident, an x-ray film showed that the heart had returned to the preoperative size, there were no symptoms or signs, and no ventricular extrasystoles were noted. Incidentally, the patient showed complete clearing of her cyanosis and was able to carry on a full schedule of household and marital duties.

Case 2 (*Fig. 2*).—F. H. was a 12-year-old boy who underwent atrial septal surgery on July 16, 1958, utilizing the open technique and hypothermia. His postoperative course was considered routine. However, because of the child's extreme apprehension he was oversedated for the first two or three days, became dehydrated, and could not be managed properly. Subsequently, he was taken off sedation and his recovery was rapid. On July 21, he again became apprehensive and restless, and on July 22, he complained of pain in his chest. Physical examination revealed a bilateral dullness over both bases which could not be differentiated from the usual postoperative dullness, and a to-and-fro friction rub was heard in the third and fourth left intercostal spaces. There was no enlargement of the liver. His hemoglobin was 13 Gm., and he had a white blood cell count of 14,300. An electrocardiogram showed moderate flattening of the S-T and T waves in Leads I and V_6. On July 24, he again had a spiking fever of 101° F. On July 25, he was somewhat improved and was considered sufficiently well for discharge and care at home. An x-ray film on July 25, showed enlargement of the cardiac shadow consistent with pericarditis. There was also increased density in the right lung region, which was greater than that seen in other

postoperative films (not shown). An x-ray film on August 26, showed complete clearing of the process. He received no special treatment and was discharged to his home on complete bed rest, with instructions to return if further symptoms occurred. On Sept. 27, he was seen again; he had no symptoms, or fever, and there were no abnormal sounds consistent with this syndrome.

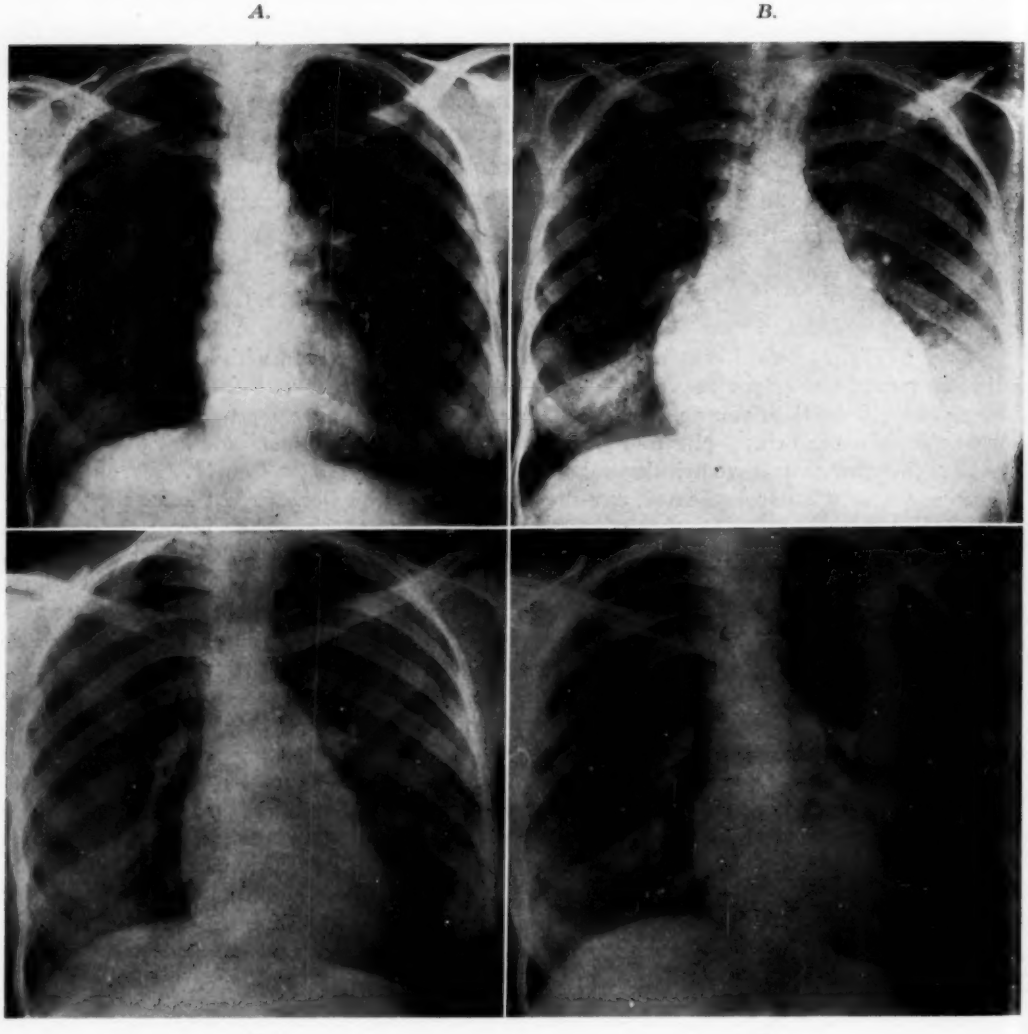

Fig. 1.—Case 1. C. S., a 25-year-old white woman with congenital valvular pulmonic stenosis. X-ray film taken: *A*, May 21, 1955. *B*, Oct. 31, 1955. *C*, Dec. 10, 1955. *D*, Oct. 27, 1956.

Case 3 (*Fig. 3*).—N. R. was a 6-year-old white girl who underwent a Brock transventricular valvulotomy, Oct. 24, 1957, utilizing mild hypothermia. Her postoperative period was essentially uneventful until October 30, except for the fact that both child and mother were extremely anxious and exaggerated her symptoms and problems out of all proportion. On October 31, seven days postoperatively, she complained of pain in her chest and was more fussy than usual. Physical examination revealed tenderness and enlargement of the liver, a tachycardia, a to-and-fro friction rub over the heart, and increased dullness of the left chest. Her hemoglobin was 9 Gm., with a white blood cell count of 11,000 and 73 per cent neutrophils. An electrocardiogram showed

flattening of the S-T and T segments, and S-T elevation in one of the chest leads. She was digitalized and placed in oxygen, with relief of her symptoms. Her symptoms continued until November 7, and she was discharged on November 9, to be cared for at home. An x-ray film taken on November 1, during the acute process, demonstrates enlargement of the cardiac shadow and increased density on both the right and left bases; another film on April 28, 1958, shows complete clearing of all processes.

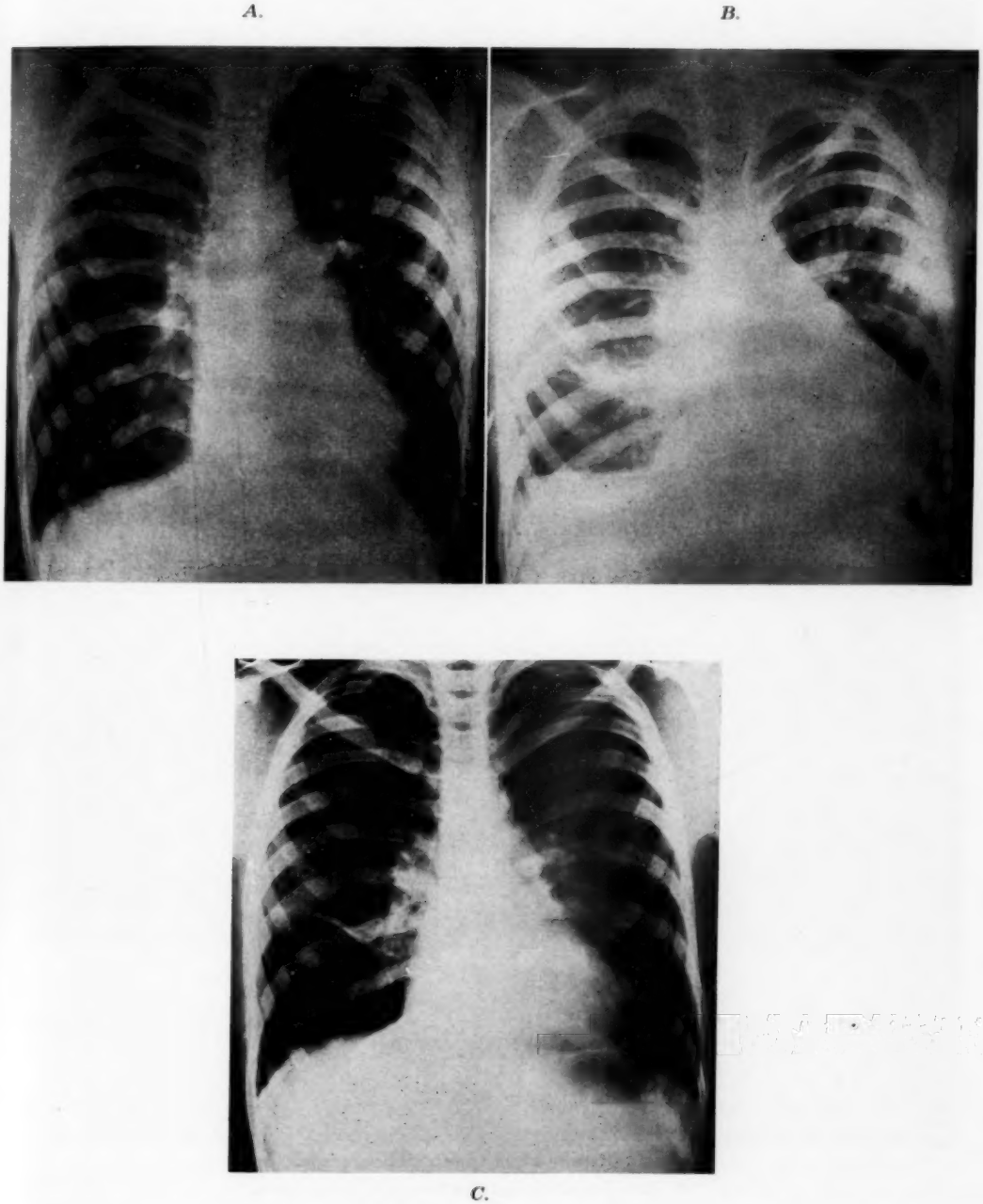

Fig. 2.—Case 2. F. H., a 12-year-old boy with atrial septal defect. X-ray films taken: *A*, Nov. 10, 1957. *B*, July 25, 1958. *C*, Aug. 26, 1958.

Case 4 (Fig. 4).—L. R. was a 17-year-old white boy who underwent an atrial septal closure o
February 2, 1955, utilizing the so-called "Bailey Donut Technique" and hypothermia. Th
postoperative course was not stormy, and the boy showed good evidence of continued recover
until March 3, twenty-nine days postoperatively. He had been discharged from the hospital an

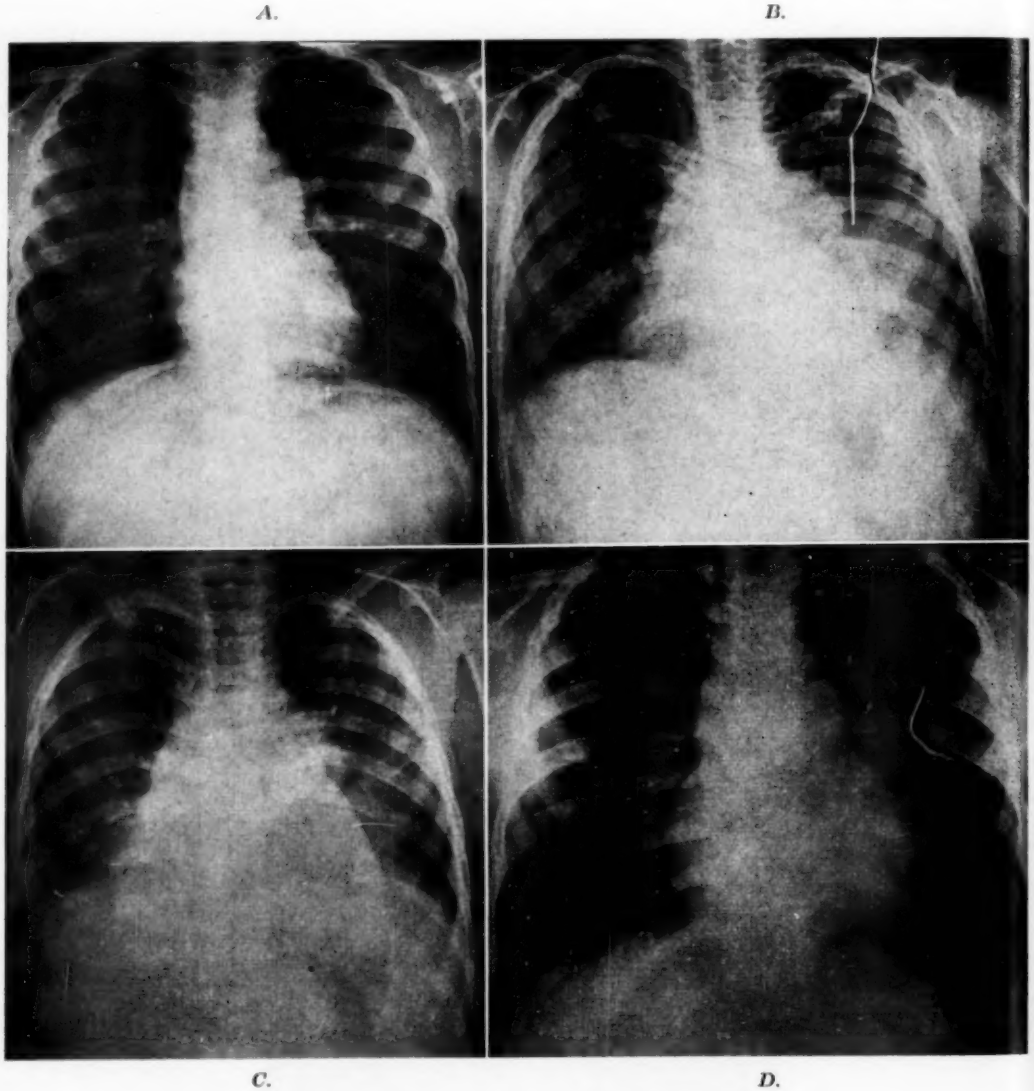

Fig. 3.—Case 3. N. R., a 6-year-old white girl who underwent a Brock transventricular valvulotomy. X-ray films taken: *A*, Oct. 22, 1957. *B*, Nov. 1, 1957. *C*, Nov. 4, 1957. *D*, April 28, 1958.

was readmitted with chills and fever, pain in the chest, and pains in the abdomen. He was coughing, and said that it was painful to breathe. Physical findings showed decreased breath sounds and dullness in the right base, and distant heart tones. The liver was enlarged and tender. There was a to-and-fro friction rub, and a spiking fever was noted over the next two days. His hemoglobin was 10 Gm., and the white blood cell count went as high as 12,700. An electrocardiogram taken on March 8, showed flattening of the S-T and T wave segments, with low voltage in the QRS. He improved, and on April 4, he was thought to be out of danger. His subsequent course

however, included fibrillation, pulmonary infarction, and subacute bacterial endocarditis. Following the heart infection he had a steady downhill course, and expired on January 21, 1956, probably as a result of the endocarditis. An x-ray taken on March 7, 1955, demonstrated the acute pericarditis, with a huge enlargement of the cardiac shadow and increased density in both chests; another film on April 4, showed a great reduction in the size of the heart and in the density of the lung fields.

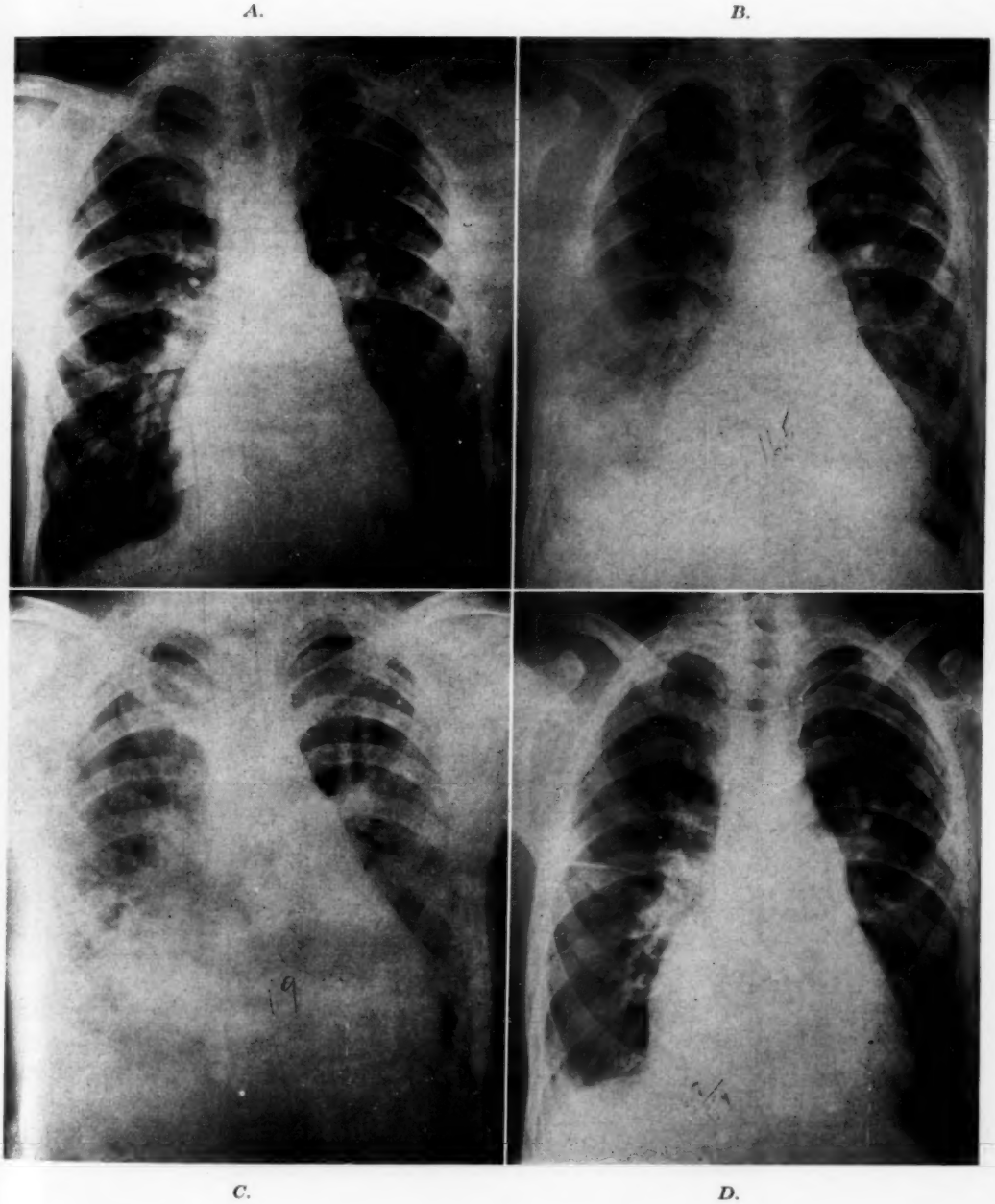

Fig. 4.—Case 4. L. R., a 17-year-old white boy with an atrial septal defect. X-ray films taken: *A*, Feb. 1, 1955. *B*, Feb. 10, 1955. *C*, March 7, 1955. *D*, April 4, 1955.

Case 5 (*Fig. 5*).—J. P. was a 6-year-old white girl who underwent a transpulmonary arter valvulotomy on May 27, 1957, utilizing hypothermia. The postoperative course was completel uneventful, and she was discharged to her home at the end of ten days. On June 12, fifteen day postoperatively, the child developed fever, vomiting, and pain in the chest. Physical examinatio revealed moderate dyspnea, enlargement and tenderness of the liver, and increased pulsation in the neck. There was a gallop murmur, best heard at the apex, and a to-and-fro friction rub ove the heart. There was a dullness to percussion, and decreased breath sounds over both base

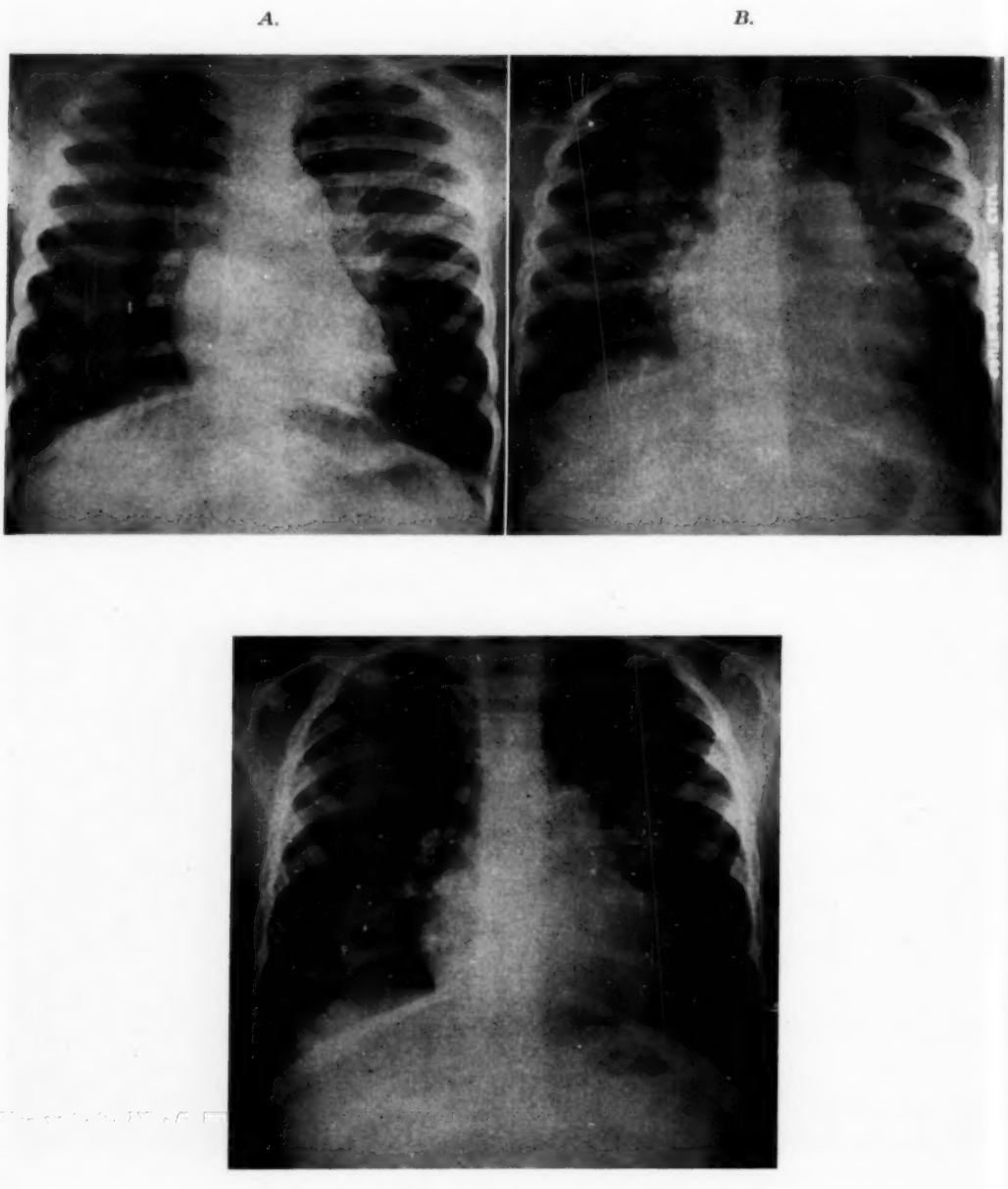

Fig. 5.—Case 5. J. P., a 6-year-old white girl who underwent a transpulmonary artery valvulotomy. X-ray films taken: *A*, May 26, 1957. *B*, June 14, 1957. *C*, May 19, 1958.

Her hemoglobin was 9 Gm., and her white blood cell count was 9,250. She continued to be symptomatic through July, 1957. On August 9, no further symptoms of fever were noted, and her exercise ability had increased greatly. An x-ray film on June 14, 1957, showed acute enlargement of the cardiac shadow.

DISCUSSION

Eleven patients with x-ray evidence of enlargement of the cardiac shadow following cardiac surgery for congenital heart lesions are presented; in all cases the pericardium was opened. The lesions involved were the usual congenital conditions requiring pericardiotomy, i.e., atrial septal defect and pulmonary stenosis. The case of aortic stenosis was exceptional, both in its severity and in the rareness of treatment of this type of lesion at this age and under hypothermia. Only one patient in this series did not show complete recovery, and his course was complicated by pulmonary infarction, subacute bacterial endocarditis, and probably a number of small coronary infarctions.

Previous reports of the postpericardiotomy syndrome describe no etiological factor except presumed trauma to the myocardium during surgery and perhaps intrapericardial bleeding. The association of pleural effusion and pneumonia is not clear, although, as noted by Dressler[3] and by Weinstein,[4] these two complications are frequent in idiopathic pericarditis. Rheumatic activity has not been observed in any of these patients, and all of them showed rapid convalescence after termination of the course of this syndrome. No patient in this series has yet exhibited any form of constrictive pericarditis.

It is difficult from the present figures to predict the exact incidence of this postpericardiotomy syndrome, because recognition varies from place to place and with each observer. It is hoped that with the attention given postoperative pericarditis it will be looked for more frequently and that a true incidence can be determined in the future.

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Auricular Infarction

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Infarction of the auricles of the heart is considered to be a rare condition and has been reported only occasionally. This may be due to the fact that the atrial infarction does not present a distinct clinical picture and is usually associated with ventricular infarction. However, the lack of a well-defined clinical picture does not rule out the possibility that atrial infarctions occur more often than has been reported. In their study of myocardial infarction, Cushing and associates[1] found 31 infarctions of the auricles in 182 cases of ventricular infarction (17 per cent), and Wartman and Hellerstein[2] found 17 atrial infarctions in 235 cases of myocardial infarction (7.3 per cent); in 4 cases the atrial infarctions were found alone without association with ventricular infarction.

The diagnosis in the clinical cases is based mainly on the electrocardiographic changes, which, however, are usually transient, indistinctly marked, and without definite diagnostic signs. It was considered of interest, therefore, to report two cases of myocardial infarction associated with atrial infarction which were verified by postmortem examination. In one case the correct antemortem diagnosis was based on the striking change of the contour of the auricular wave.

CASE REPORTS

CASE 1.—Case 1 was that of a 65-year-old housewife who was admitted to the hospital about 6 hours after a severe attack of precordial pain. She gave a 2-year history of chest pain on exertion, shortness of breath, and swelling of ankles and legs.

On admission to the hospital the patient was pale and perspired profusely. Her blood pressure was 180/120 mm. Hg; it dropped 2 hours later to 135/75 mm. Hg. The heart was slightly enlarged to the left. A loud systolic murmur was audible in the mitral area. The neck veins were not markedly distended. There was pitting edema of the feet, ankles, and legs.

An electrocardiogram (Fig. 1) obtained about 6 hours after the attack showed regular sinus rhythm occasionally interrupted by auricular extrasystoles. The P wave was strikingly split, flattened, and broadened in limb and chest leads. The initial part of the auricular complex was directed downward, appearing as a broad Q_a wave. A slight elevation of the P-T_a segment in Leads I and II was evident. In the chest leads the P wave was inverted, peaked, and notched in Lead V_1 and split and flattened in Leads V_2 through V_6. The remainder of the electrocardiogram showed a minute R in Leads V_1 through V_4. The tracings indicated an old anteroseptal infarction, and, as judged from the striking abnormalities of the auricular complex, an atrial infarction also. The patient died suddenly at night about 10 hours after admission to the hospital.

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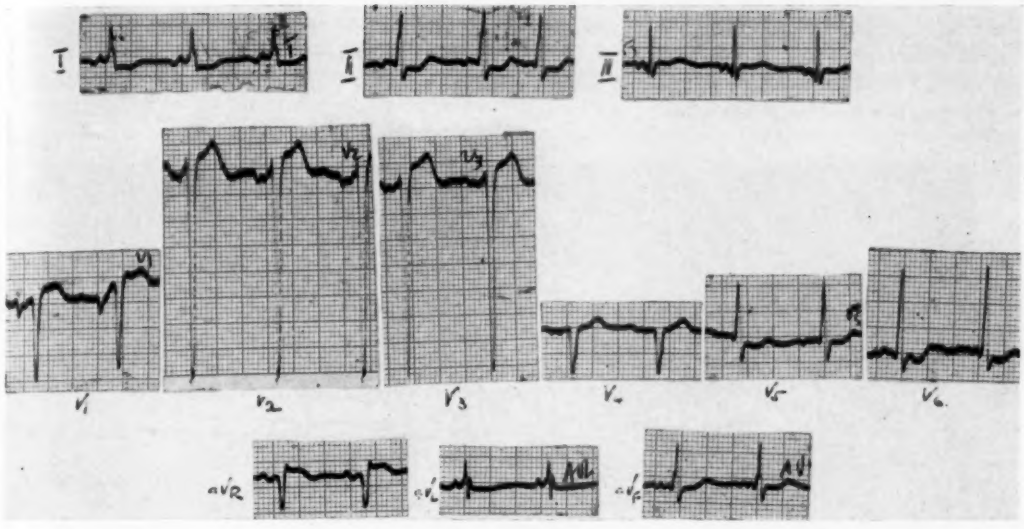


Fig. 1.—See text.

Fig. 2.—Marked arteriosclerotic narrowing of the lumen of the auricular branch of the left circumflex artery.

Autopsy.—Postmortem examination revealed generalized arteriosclerosis involving mainly the aorta, coronary, mesenteric, iliac, and renal arteries. There was an old thrombosis of the superior portion of the descending branch of the left coronary artery. In addition, there were old pericardial adhesions, acute pulmonary edema, chronic passive congestion of the lungs, chronic pyelonephritis, and nephrosclerosis.

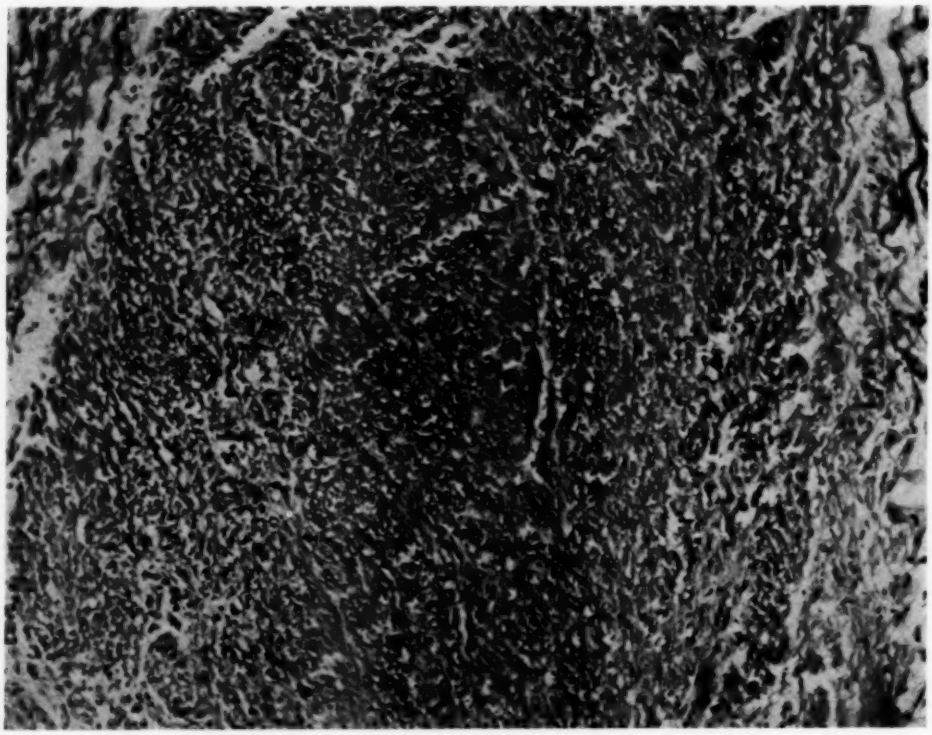


Fig. 3.—Section of the anterior wall of left auricle showing smudging of fibers, and loss of muscle nuclei and striations.

The heart weighed 520 grams. The left ventricular wall measured 1.8 cm. in thickness, and the right, 0.5 cm. The pericardium was markedly adherent to the epicardium. The endocardium was smooth and shiny. The myocardium of the apical third of the anterior left ventricular wall was rather soft to the touch, but on cross section it appeared normal. Another small area of softening was present in the middle third of the septum. High up in the anterior wall of the left ventricle there was an area, measuring 3 by 4 cm., which showed several white streaks and patches of fibrous tissue. The left auricle appeared to be moderately dilated. The anterior wall of the left auricle near the interauricular septum was flabby and showed an area, approximately 1 by 1 cm., of reddish-brown discoloration, in which the muscle fibers were poorly defined.

All the large branches of the coronary arteries were arteriosclerotic, containing several small calcified plaques. The descending branch of the anterior coronary artery was occluded by an old organized thrombus just distal to its origin and extending 0.5 cm. downward. Farther down, the artery was patent and so were both branches to the apex of the left ventricle and to the septum. The left circumflex artery and its branch to the left auricle did not show any evidence of thrombosis, but the lumina of both arteries were markedly narrowed (Fig. 2). The right auricle and right ventricle, as well as the aortic, mitral, tricuspid, and pulmonary valves, were unremarkable.

Microscopic Description.—Sections through the apex of the left ventricle and septum were unremarkable. Sections through the upper portion of the anterior wall of the left ventricle showed several areas of focal fibrosis consistent with an old myocardial infarction. Sections through

the anterior portion of the left auricle (Fig. 3) showed smudging of fibers, a brick-red discoloration, and loss of muscle nuclei and striations consistent with the early changes of a myocardial infarction.

CASE 2.—Case 2 was that of a 68-year-old woman who complained of vague epigastric pain for 2 months previous to admission to the hospital. The physical and radiologic findings were normal. The blood pressure was 150/80 mm. Hg.

The electrocardiogram (Fig. 4) showed regular sinus rhythm; the P waves were split, notched, and flattened and were inverted in Leads II and III as well as in the chest leads. The P-T_a segment was depressed in all leads. The remainder of the electrocardiogram showed diffuse myocardial damage without signs of a focal lesion.

Fig. 4.

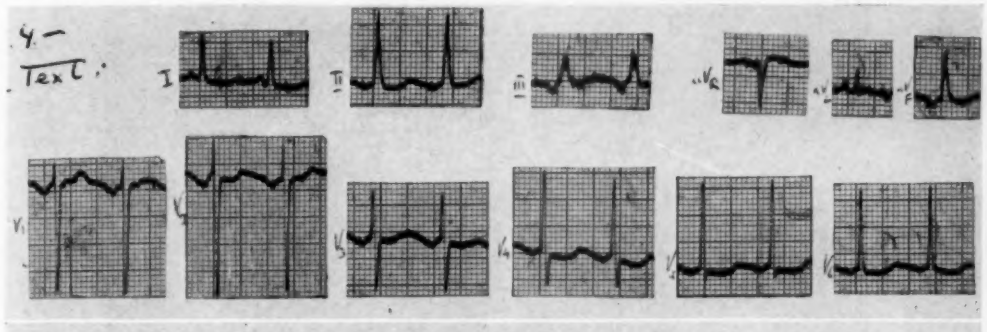
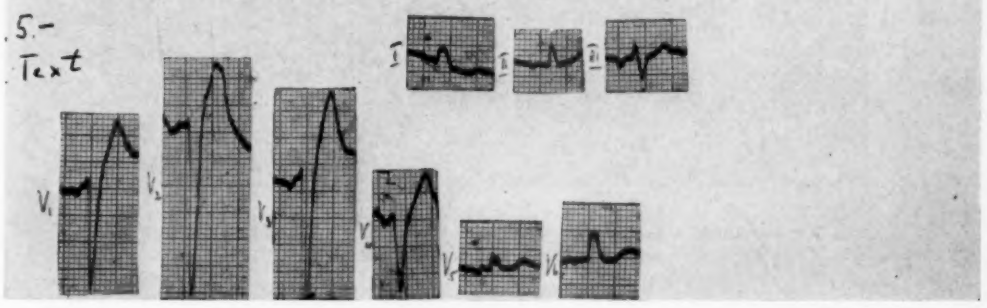


Fig. 5.



Figs. 4 and 5.—See text.

One day later the patient suffered severe epigastric pain and vomiting. Blood pressure dropped to 80/65 mm. Hg. The electrocardiogram (Fig. 5) showed left bundle branch block and signs of an acute anteroseptal infarction. The P waves remained inverted, split, and flattened.

The patient died the following day.

Autopsy.—Postmortem examination revealed generalized arteriosclerosis involving mainly the coronary arteries, aorta, iliac, renal, and mesenteric arteries. There was a recent myocardial infarction involving the anterior wall of the left auricle and left ventricle. In addition, there was an old myocardial infarction of the interventricular septum.

The heart weighed 400 grams and was markedly flabby and soft. The left ventricular wall measured 0.9 cm. in thickness; the right, 0.3 cm. The pericardium and the endocardium showed no abnormalities. The epicardium of the anterior wall of the left ventricle showed marked congestion, especially in its upper third. The myocardium of the whole anterior wall of the left ventricle was very soft to the touch, and on cross section it showed marked reddish discoloration and loss of the normal appearance of the muscle fibers. The region of red discoloration and the changes in the muscle fibers extended upward into the anterior wall of the left auricle near the interauricular septum. The upper third of the interventricular septum showed a few white patches of connective tissue within the muscle fibers.

The anterior descending coronary artery showed moderate arteriosclerosis. The left circumflex branch of the anterior coronary artery was markedly arteriosclerotic and showed extreme narrowing of the lumen. A small calcified plaque was found partly blocking the lumen of this artery at its origin. This plaque extended into the lumen of the descending branch of the anterior coronary artery. The posterior coronary artery, the right auricle and ventricle, as well as the mitral, aortic, tricuspid, and pulmonary valves, appeared to be normal.

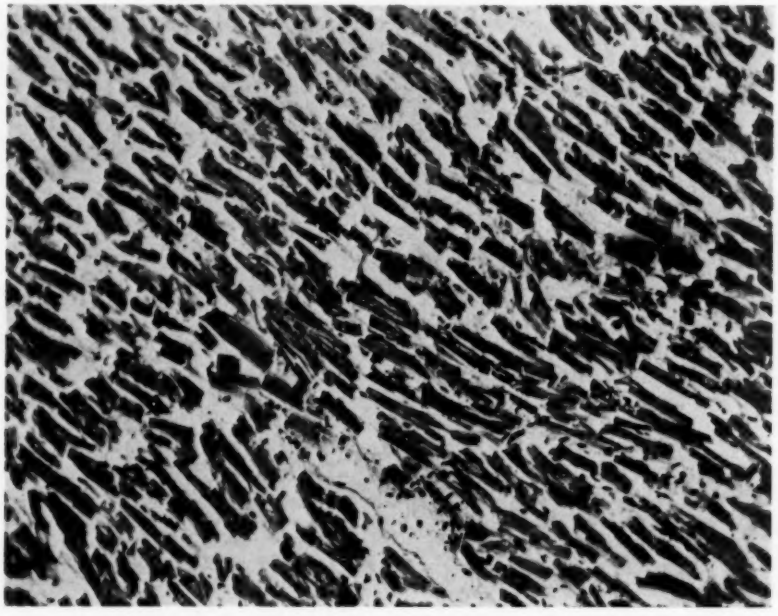


Fig. 6.—Section of anterior wall of left auricle showing marked fragmentation and separation of muscle fibers.

Microscopic Description.—Sections taken through the left ventricle showed some smudging and marked fragmentation, with separation of the muscle fibers and a slight degree of loss of architecture, very slight infiltration of polymorphonuclears, and some hyperemia. Sections through the left auricle showed also smudging of the fibers, fragmentation, and slight infiltration of polymorphonuclears (Fig. 6). These changes are consistent with a recent myocardial infarction. Sections through the upper third of the interventricular septum showed several areas of focal fibrosis consistent with an old myocardial infarction.

DISCUSSION

The electrocardiogram of a 65-year-old patient taken a few hours after a severe anginal attack showed signs of an old anteroseptal infarction. There were no changes in the QRS complex or in the T wave indicating a recent ventricular lesion as the clinical picture would have suggested. The P waves, however, in the limb leads and in the chest leads were strikingly deformed, presenting a split, broadened, and flattened shape. The initial part of the auricular complex was directed downward, appearing as a Q_a wave. Besides the abnormal shape of the P wave, there was a slight elevation of the P-T_a segment in Leads I and II, and inversion of the P waves in the chest leads. These changes of the auricular

complex indicated an intra-auricular disturbance, and, in association with a clinical picture of acute coronary occlusion, were suggestive of an atrial infarction.

In the second case the P waves were also split, flattened, and inverted, mainly in Leads II and III and in the chest leads. The P-T_a segment in Leads II and III and in the chest leads was not elevated, but markedly depressed. In this case the abnormalities of the auricular complex were associated with changes in the QRS complex and the T wave, which indicated acute ventricular infarction, and the abnormal P waves appeared to be a sign of an auricular stress.

The diagnosis of auricular infarction is commonly based on a disturbed auricular mechanism, deviation of the P-T_a segment, and abnormal shape of the P wave. These abnormalities may occur together or alone and are usually transient. The abnormal auricular mechanism occurs as an attack of auricular fibrillation or flutter, as frequent auricular extrasystoles, or as a nodal rhythm. It is of interest to note that while the majority of reported atrial infarctions have been found in the right auricle, in both of our cases the infarction was in the left auricle, regular sinus rhythm was present, and only occasional auricular extrasystoles were noted (Case 1).

Deviation of the P-T_a segment is manifest either as an elevation or as a depression of this segment and has been found in clinical[3-8] as well as in experimental studies.[9-11] In cases of infarction of the left auricle, elevation of the P-T_a segment in Lead I, and in cases of infarction of the right auricle, elevation as well as depression of the P-T_a segment in Leads II and III has been reported. According to Hellerstein,[7] the direction of P-T_a deviation depends on the location of the infarct. In infarction of the posterior wall of the right auricle the P-T_a segment in Leads II and III has been found elevated, while in infarction of the anterior wall the P-T_a segment was depressed. It is probable that the direction of P-T_a deviation depends also on the duration of the infarct. As in acute ventricular infarction, transient changes in the ventricular complex occur, so in the early stages of an atrial lesion, elevation of P-T_a may be present, and after a few hours or days it may subside and change into a depression. In our first case, in which P-T_a was elevated, the infarct was approximately 6 hours old; while in the second case, in which the P-T_a was depressed, the infarct was about 24 hours old.

Considering the fact that the depression of P-T_a may also occur in tachycardia, the deviation of P-T_a per se does not warrant a diagnosis of atrial infarction unless it is associated with an abnormal P wave. Changes in the P wave have rarely been looked upon as diagnostic signs of myocardial lesion. A split, notched P wave has been mentioned as a finding in atrial infarction, but the disturbed auricular mechanism and deviation of P-T_a are more often emphasized in atrial lesion. An increase in amplitude and widening of the P wave in patients with acute coronary occlusion has been described and considered to be a sign of auricular dilatation following acute ventricular infarction.[12] However, no postmortem findings were reported. In experimentally induced, localized left auricular necrosis, Sanders[10] has obtained a deep auricular Q_a wave with elevation of P-T_a in Lead I. In our cases also the P waves revealed a marked

Q_a wave (Case 1) and were flattened, split, and inverted, with a deviated P-T_a segment. It appears therefore that in a patient with an acute coronary occlusion, changes in the auricular complex should be considered as a strong indication of an acute atrial lesion.

SUMMARY

Two cases of atrial infarction, verified by postmortem examination, are presented. The correct antemortem diagnosis was made in one case on the basis of the abnormal contour of the auricular complex.

The significance of the electrocardiographic changes in atrial lesion is discussed.

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Electrocardiographic Studies in Asian Influenza

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Recently, there has been renewed interest in the cardiovascular complications of epidemic viral diseases. Evidence of cardiac abnormality has been demonstrated in infectious hepatitis,[1] infectious mononucleosis,[2] poliomyelitis,[3] atypical pneumonia,[4] measles,[5] mumps,[6] and diseases caused by group B Coxsackie viruses.[7-9] Except in very young infants these complications have usually been transitory and have been attributed to myocarditis on the basis of minor changes in the electrocardiogram, usually of the S-T and T components. Disorders of the conduction system have also been noted.

Comparable studies during influenza epidemics have been relatively few, and in most instances have been based on individual cases; only rarely has the presence of associated infection by influenza virus been adequately confirmed. The object of the present investigation was to determine the incidence of cardiovascular involvement in patients during and following illness associated with infection by type A influenza virus, "Asian" strain, as shown by clinical appraisal and electrocardiographic examination.

MATERIALS AND METHODS

One-hundred and one male students, ranging in age from 17 to 29 years, were studied during the influenza epidemic in October, 1957. They represented consecutive patients admitted to the infirmary at the University of North Carolina with a diagnosis of influenza. At the time of admission a history was obtained and physical examination performed with particular emphasis on the cardiovascular system. In addition, a standard 12-lead electrocardiogram was taken, and repeated on alternate days thereafter until the time of discharge. A Sanborn Viso-Cardiette was used. Analyses of the electrocardiograms were made by contrasting the records taken on admission with those obtained at the time of a follow-up visit 1 to 4 months later. These tracings made during illness and recovery were then compared with those of 150 normal male subjects from the same student population who had been investigated previously by Gottschalk and Craige.[10] Originally, the records of these "controls" had been studied primarily for their precordial configuration. In the present study the same records were re-examined in order to make additional observations and comparisons pertinent to the findings in patients with influenza. These included

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rate, rhythm, P-R interval, QRS axis, Q-T_c,[11] S-T deviations, and T-wave height. S-T segments were reported to be elevated or depressed depending on whether they fell above or below the isoelectric line. The latter was taken as the T-P line.[12]

Roentgen films of the chest were taken on 25 patients and were repeated when an abnormality was found.

Laboratory studies included routine blood counts and urinalyses, as well as cultures of the throat for bacterial pathogens. Samples of blood, collected early in the acute illness and during convalescence, were stored in a frozen state for determinations of antibody against influenza viruses.

Medication consisted only of aspirin as required for symptomatic relief, and tetracycline in 20 patients whose abnormal physical signs, symptoms, or radiologic findings suggested pulmonary disease.

Following discharge, patients were permitted to resume their normal activities, but were required to return in 1 to 4 months for a repetition of the physical examination, electrocardiogram, and collection of blood for serologic study. A careful interval history was elicited in order to eliminate individuals who had suffered another respiratory or influenza-like illness during the interval between discharge from the infirmary and the return visit.

Specimens of blood were allowed to clot; after centrifugation the serum was removed and stored at −20° C. until tested. Successive specimens of serum from each patient were tested simultaneously by the hemagglutination-inhibition technique.[13] At the time of the test the serums were diluted in normal saline to an initial dilution of 1 to 4 and were inactivated at 56° C. for 30 minutes. Serial twofold dilutions of serum were prepared from dilution 1 to 4 through dilution 1 to 256. All serums were tested against three antigens: (1) A/JAP/305/57, early egg passage; (2) A/Formosa/313/57, early egg passage. (These two strains were obtained from Dr. G. P. Manire.) (3) A/JAP/305/57, egg-ferret-mouse-egg animal line (obtained from Dr. Keith Jensen).

RESULTS

Laboratory.—While the early egg-pass material was of lower viral titer, and, in general, gave lower hemagglutination-inhibition titers, the results were quite clear-cut. It was noted that the serums of some patients would react with the 305 antigen and not with the 313, while the pattern of reaction was reversed in the serums of other patients.

The 87 cases herein reported all exhibited an increase in antibody against influenza virus, as indicated by a fourfold or greater rise in the hemagglutination-inhibition titer in the specimen of serum collected during convalescence when compared with that of the initial specimen. Indeed, no antibody was detectable in the initial serum from most of these patients at the limiting 1 to 4 dilution.

Clinical.—The 87 patients with Asian influenza were only mildly ill. Symptoms were uniform in the group and consisted of cough, malaise, headache, and dizziness. There were no symptoms of thoracic pain, palpitation, or dyspnea. Physical signs included fever in all patients, but it was of brief duration following admission, being present on an average of only 2 days, with a range of from 1 to 5 days. The sclerae and conjunctivae were often found to be hyperemic. No abnormalities of the heart or blood pressure were detected. Adventitious sounds were noted on examination of the respiratory system in a few individuals, but these were transient. The average period of hospitalization was 3 days.

Electrocardiograms.—Analyses were made of the tracings recorded initially and after recovery, during a follow-up visit 1 to 4 months later. The tracings from each patient were compared, and the findings were also compared with those of the normal control group of 150 University students from the same popu-

lation. It was found that the electrocardiograms made on alternate days during illness did not differ significantly from the initial record, and therefore the statistical analyses discussed below are drawn from the admission tracings, those made on recovery, and the normal controls.

The heart rate during illness showed a mean of 74.4, with a range of 45 to 120. The rate in recovery showed a mean of 75.4, with a range of 47 to 115. The difference was not statistically significant and also did not differ significantly from the mean rate of the normal controls, which was 73.8, with a range of 46 to 111.

No abnormalities of rhythm were noted during illness. The recovery records, however, included two examples of wandering of the pacemaker within the sinus node, and one example of intermittent high auriculoventricular nodal rhythm.

There were no instances of prolongation of the P-R interval in any of the records of the subjects or controls.

TABLE I. MEANS AND VARIANCES FOR T-WAVE HEIGHTS AND Q-Tc IN 87 WHITE MALE PATIENTS WITH ASIAN INFLUENZA AND 150 NORMAL WHITE MALES

COMPONENT OF CARDIOGRAM	MALE PATIENT (87)						NORMAL MALES (150)	
	ILLNESS		RECOVERY		ILLNESS MINUS RECOVERY		MEAN (MM.)	S^2 (MM.^{2})
	MEAN (MM.)	S^2 (MM.^{2})	MEAN (MM.)	S^2 (MM.^{2})	MEAN (MM.)	S^2 (MM.^{2})		
T-Wave Lead								
I	1.91	0.501	1.94	0.566	−0.03	0.281	1.84	0.536
II	2.64	1.394	3.06	1.380	−0.42	0.749	2.81	1.120
III	0.83	0.894	1.24	1.011	−0.41	0.600	1.04	0.909
V_1	0.78	2.184	0.92	2.639	−0.14	1.154	0.63	2.763
V_2	6.03	4.897	7.30	7.061	−1.27	3.929	6.70	6.661
V_3	5.39	4.427	7.07	6.112	−1.68	3.337	6.96	6.835
V_4	4.45	4.163	6.25	5.697	−1.80	3.770	6.00	5.930
V_5	3.40	2.331	4.52	3.160	−1.12	2.370	4.18	2.937
V_6	2.57	1.298	3.09	1.623	−0.52	1.101	2.62	1.262
Q-T_c Interval	0.400	0.0006	0.410	0.0007	−0.010	0.0008	0.419	0.0005

The Q-T_c interval was found to be slightly shorter in illness than in recovery (Table I). The mean Q-T_c during recovery, in turn, was slightly shorter than that of the normal controls. The difference between the means of each of these groups, however, was only 0.01 second, which was within the range of the error of the method of measurement.

The QRS axis fell within the normal range in the three groups (illness, recovery, and control), and no significant change occurred during the course of the illness.

The S-T segments were studied in the standard limb leads and in the precordial leads. It was noted that among the 150 controls there were S-T devia-

tions exceeding 1 millimeter in only two instances. However, among the 87 subjects, there were five such instances during illness, and six on recovery. These consisted principally of S-T elevations in the precordial leads. An example is illustrated in Fig. 1.

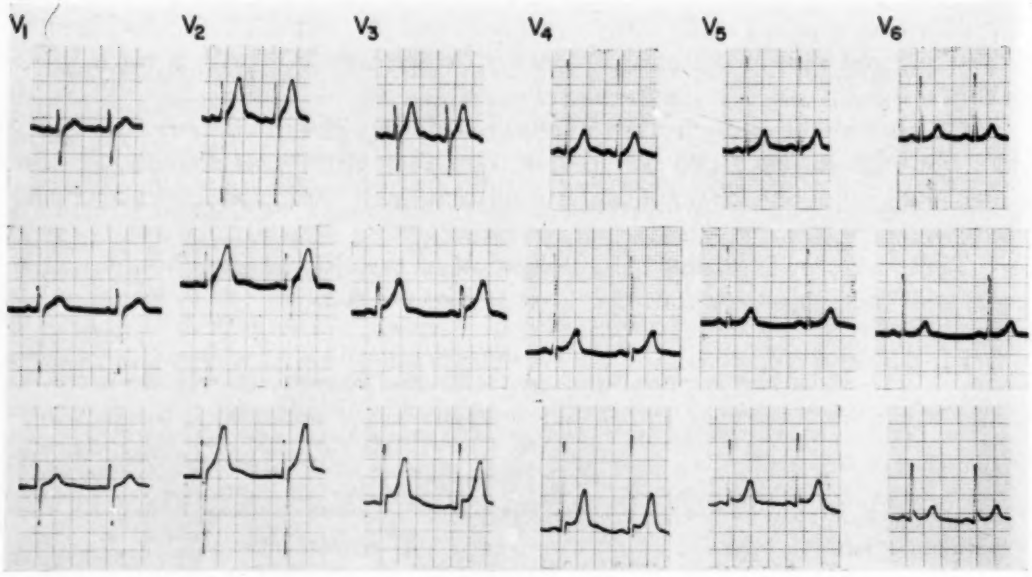

Fig. 1.—Serial electrocardiograms showing S-T elevation in Lead V_3 during illness (tracing of Oct. 26, 1957), and persisting in recovery (tracing of Nov. 25, 1957). Lead V_4 in the recovery tracing is also outside normal limits. *Top:* Oct. 24, 1957. *Center:* Oct. 26, 1957. *Bottom:* Nov. 25, 1957.

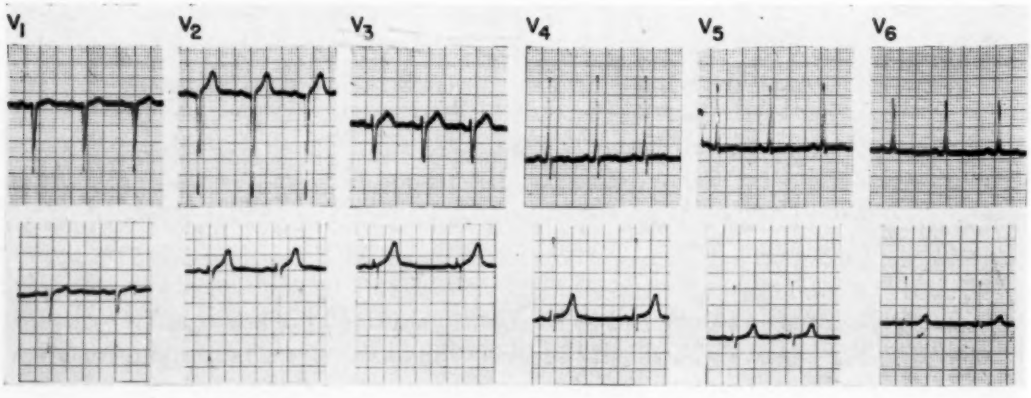

Fig. 2.—Serial electrocardiograms showing typical flattening of the T wave in Leads V_{4-6} during illness, with return to normal one month later. *Top:* Oct. 21, 1957. *Bottom:* Nov. 19, 1957.

Analysis of T-wave height was restricted to the three standard leads and six precordial leads, V_{1-6}. The results are shown in Table I. All T-wave means, except in Leads I and V_1, were significantly lower in illness than in recovery. Between T-wave height on recovery and in normal controls, however, there

were significant differences only in Lead V_6. Nevertheless, every T-wave mean was higher for the influenza patients after recovery than for the normal individuals.

There were four individual tracings in which the T waves were considered to be abnormally low, mainly in the left-sided precordial leads, and in all of these the R-T ratio was greater than 10:1. An example of one of the records showing low T waves during illness is given in Fig. 2.

Roentgenograms.—No abnormality of the cardiac silhouette was noted. Small areas of pulmonary consolidation were noted in only five instances. These changes, however, were transient. In two of these five, cultures of the throat yielded colonies of pneumococcus.

DISCUSSION

Following the influenza epidemic of 1889, there were reports that the disease had affected the cardiovascular system. Stengel,[14] in 1918, maintained that cardiovascular sequels were particularly frequent at that time, and recalled the publication of Sansom,[15] who had described various forms of cardiac irregularities as a consequence of influenza. Stengel also believed that more so-called cardiac depression resulted from the epidemic of 1889 than from that of 1918, possibly because older people mainly were affected. Postinfluenzal debility was a common diagnosis and was often attributed to impairment of myocardial function.[16] It was felt that disorders of the conduction system were also frequent, and Hamburger[17] stated that these were as pathognomonic of influenza as mitral stenosis of rheumatic heart disease. Finland and associates[18] reviewed the literature up to 1945, in a paper describing two fatal cases of acute myocarditis attributed to infection with type A influenza virus. From this review it is apparent that, from both the clinical and pathologic standpoints, there was lack of unanimity that the cardiovascular system was specifically involved in the disease. In addition, it was difficult to evaluate earlier reports because serologic studies were not available to confirm the diagnosis of influenza, and the significance of secondary infection, especially of the respiratory system, was not always taken into account. There was a considerable degree of selection because nearly all cases were in hospitals, usually because their illnesses were more severe than usual, and there were no adequate electrocardiographic studies on average or "run-of-the-mill" patients. Although it might be assumed that the incidence of cardiovascular complications would be higher in hospitalized patients, it has been stated frequently that such complications are not related to the severity of the illness, and may appear in the average case.

Since Finland's review few relevant papers have been published. Borden[19] reported a case of acute myocarditis which he attributed, on serologic grounds, to infection with type A influenza virus. Heinecker and Kemper[20] found a high incidence of abnormal electrocardiographic changes in hospitalized patients of all ages, 31.5 per cent of 154 during the Influenza-A epidemic of 1952-53, and 50 per cent of 116 during the Influenza-B epidemic of 1954-55. Myocarditis of obscure etiology has been studied at the Michael Reese Hospital by Silber,[21] and of 21 cases, four were considered to be due to influenza viruses. So far there

have been three reports concerning cases showing electrocardiographic changes in the recent Asian influenza epidemic. Bell and associates[22] were able to show no abnormality in electrocardiograms before and during the illness in 23 volunteers who had artifically induced Asian influenza. Datey and Mody[23] described electrocardiographic changes in Asian influenza. Serial electrocardiograms taken on 25 patients showed definite changes in 13. These consisted of S-T segment depression, flattening or inversion of the T waves, and ventricular and supraventricular premature beats. These changes reverted to normal, and the authors concluded that in spite of the absence of clinical evidence of myocarditis, electrocardiographic evidence of involvement of the heart was present in 11 patients. An even higher proportion of electrocardiographic changes has been found by Walsh and co-workers,[24] who studied the effects of Asian influenza on the cardiovascular system in 30 patients who had no previous evidence of heart disease. Approximately three fourths of these patients showed electrocardiographic abnormalities usually affecting the T waves. In 16 of 20 in whom serial vectorcardiograms were recorded there was mild distortion of the QRSs $\hat{E}$ loop, probably reflecting alterations in depolarization produced by subtle injury. The wide variation in the proportion of patients with abnormal electrocardiograms in these three series is most likely related to selection, and is similar to discrepancies in previous reports concerning other influenza epidemics.

In order to evaluate the results of the present investigation, it is important to consider, first, the normal standards used, and, second, the influence of extracardiac factors known to produce electrocardiographic changes. Because no other study was as comparable to that of the influenza patients in respect to age, sex, and social distribution, our normal standards were based on the electrocardiograms of 150 healthy, adult, male students previously taken at this hospital.[10] For the precise interpretation of serial electrocardiograms, intra-individual diurnal variation must be taken into account. This has been studied by Simonson and associates[25] in 12 normal young males over a period of two months, using standard leads and $CF_{1,2,4}$. The 90 per cent expectancy ranges of intra-individual variabilities were evaulated for certain components of the electrocardiogram. These findings were applied to T-wave changes between illness and recovery in our patients, assuming the CF leads to be equivalent to V leads. Although, except in Leads I and V_1, there was a statistically significant elevation of T waves in the recovery tracings as compared with the illness tracings, this could be explained by intra-individual variation in all leads except Lead V_4, in which T-wave recovery was outside normal limits in 19 of 87 patients. Standards for Leads V_3, V_5, and V_6 were not available, and therefore could not be assessed.

Extracardiac factors were also considered. Disturbances of electrolyte and fluid balance were unlikely to occur during such a brief and relatively mild illness in previously healthy individuals. The only drug commonly used was aspirin, which was given in small dosage and during a period too brief to give rise to a respiratory alkalosis. No patient had hypotension, and all electrocardiograms were taken in a standard recumbent position and not following a recent meal.[26] There have been reports on the effect of artificially induced pyrexia on the elec-

trocardiogram,[27-30] especially as it modifies the S-T segment and lowers the R and T waves. These changes have been attributed to alterations in rate and position of the heart, and the effect of respiratory alkalosis due to hyperpnea. In this study, electrocardiographic abnormalities which occurred in febrile patients persisted in tracings taken after the temperature returned to normal. This was interpreted as evidence that pyrexia was not responsible for the changes found.

Taking all these factors into consideration, there were 12 patients with abnormal electrocardiograms, five with S-T segment changes, four with T-wave changes, and three with arrhythmias. These are summarized in Table II. None of these patients had any distinguishing features in the clinical course of the disease, or on the follow-up examination, apart from one who had evidence of minor respiratory involvement.

TABLE II. SUMMARY OF ELECTROCARDIOGRAPHIC CHANGES IN 12 PATIENTS WHO HAD ASIAN INFLUENZA

ILLNESS	RECOVERY
1. S-T depression in Lead III	Normal
2. Slight S-T elevation in Leads V_{4-5}	S-T elevation in Lead V_4
3. Normal	S-T depression in Lead II
4. S-T elevation in Lead V_3	S-T elevation in Leads V_{3-4}
5. S-T elevation in Leads V_{2-3-4}	S-T elevation in Leads V_{4-5}
6. T flat in Leads I, II, III, V_6	T flat in Lead V_6
7. T flat in Leads V_{5-6}	Normal
8. T flat in Leads V_{4-5-6}	Normal
9. T flat in Leads V_{4-5-6}	T flat in Leads V_{4-5-6}
10. Normal	Wandering pacemaker
11. Normal	Wandering pacemaker
12. Normal	High nodal rhythm

It appears that the findings of this investigation are probably representative of electrocardiographic changes in average patients who would not ordinarily be admitted to a hospital. It is obvious that these changes are minor, but they would satisfy the criteria that Fine and associates[28] laid down for an electrocardiographic diagnosis of myocarditis. It is of interest that four of 12 patients had electrocardiographic changes in the recovery tracing only, and that these included all the arrhythmias which were encountered. This agrees with the observation that cardiovascular complications of influenza are common during convalescence and even later. Two of Silber's cases of myocarditis were likewise delayed.[21] The observations reported reveal a surprisingly high incidence of minor electrocardiographic changes, both during and following Asian influenza, which could well be attributed to the disease itself.

SUMMARY

Eighty-seven University of North Carolina students who had clinical and serologic evidence of infection with type A influenza viruses related to Asian

strains were studied electrocardiographically, both during the illness and after recovery. The electrocardiograms were evaluated by comparison with those of a control series similar in age, sex, and social distribution. Extracardiac factors were taken into consideration. Twelve electrocardiograms were considered to be abnormal because of S-T segment deviation, depression of T waves, and auricular arrhythmias. Four of these abnormalities, including all the arrhythmias, occurred in the recovery stage. It was concluded that although these changes were minor, they could have been caused by myocarditis due to infection with influenza virus.

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Recatheterization of the Right Heart in Ventricular Septal Defect

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What may be in some individuals the chief complication in the natural history of a ventricular septal defect is the development of pulmonary vascular changes, functional or anatomic, or both, which serve to increase resistance to pulmonary flow.

In order to secure an estimate of the rate of progression of these changes as measured by rise in right ventricular and pulmonary pressure, the records of 20 patients with ventricular septal defect in whom right heart catheterization was repeated 17 months to 8 years following the initial study were reviewed.

PATIENTS AND METHODS

In all 20 individuals the sole demonstrable defect was one of the ventricular septum, there being a step-up in oxygen content of 1 volume per cent or more from right atrium to right ventricle. Excluded were those patients with even a minimal gradient in systolic pressure between right ventricle and pulmonary artery, those in whom the catheter tip passed on either occasion from right atrium to left atrium even though no shunt at the atrial level could be determined, those in whom an additional defect was suspected although not demonstrated, and those in whom the second catheterization failed to support the evidence of an interventricular shunt furnished by the first.

There were 10 males and 10 females. The age at the time of the initial catheterization ranged from 6 weeks to 13:9 years (average 3:7 years); that at the second catheterization, from 19 months to 17:5 years (average 7:1 years). The average interval between catheterizations was 3:8 years (Table I).

On both occasions the study was performed during sleep induced by sodium Pentothal.

All oxygen determinations were made with the Van Slyke apparatus. At least two blood samples were secured from the cavae, three from the right atrium, two or three from the right ventricle, and two from the pulmonary circuit. Arterial blood was obtained from a peripheral vessel.

Pressure was recorded continuously as the catheter tip was withdrawn from the pulmonary artery through the right heart, except when samples were being drawn. In some patients an electromanometer and direct polyoscillograph (Sanborn) was used for the first study, a strain-gauge manometer and a photo-oscillograph (Electronics for Medicine) for the second. Both instruments were calibrated against a mercury manometer.

Each patient was seen at intervals of 1 or 2 years after the initial catheterization. On each occasion a detailed history of signs and symptoms was obtained and a careful physical examination made.

Repeat x-ray studies and electrocardiograms were secured only at the time of the second catheterization.

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TABLE I. DATA ON 20 PATIENTS RECATHETERIZED AT INTERVALS OF 17 MONTHS TO 8 YEARS

PATIENT	AGE	INTERVAL (YR.)	OXYGEN CONTENT (VOL. %)			PRESSURE (MM. Hg)		
			RA	RV	PA	RV	PA	SA
A.D.	8 yr. 11 yr.	3	10.7 13.1	13.0 14.5	13.0 15.0	55/0 58/0	55/40 60/35	90/60 98/62
F.M.	13:9 yr. 17:5 yr.	3:8	13.3 15.5	14.6 17.5	15.1 18.3	94/0 71/0	90/64 70/33	120/64 81/50
P.J.	10:6 yr. 12 yr.	1:6	10.5 10.7	14.5 13.5	14.5 13.7	90/0 62/3	90/40 62/33	115/85 86/48
J.I.	10 wk. 4:3 yr.	4:1	5.4 8.8	10.8 9.9	9.9 10.3	40/0 30/0	40/15 30/10	85/50 95/50
E.M.	3:2 yr. 5:10 yr.	2:8	10.9 11.9	13.8 14.4	13.9 14.0	22/0 25/0	20/10 25/10	105/60 127/90
A.R.	3 mo. 1:10 yr.	1:7	9.5 11.1	10.8 12.3	11.0 12.2	60/0 29/0	60/20 29/10	75/55 80/60
M.B.	7 wk. 4:9 yr.	4:7	5.4 12.8	9.5 13.9	9.7 13.0	50/0 22/0	50/20 20/6	— —
A.B.	4 mo. 2:5 yr.	2:1	4.3 9.7	9.6 13.2	10.1 13.2	70/0 80/0	70/40 80/50	70/50 100/60
R.M.	2:3 yr. 4:9 yr.	2:6	11.1 12.8	12.7 13.8	13.3 13.5	50/0 50/0	50/20 50/25	90/45 100/60
R.H.	8 mo. 8:11 yr.	8:3	10.3 10.7	12.0 12.1	12.1 12.0	25/0 22/0	25/5 22/10	100/60 108/58
J. R.	4 yr. 7:1 yr.	3:1	10.7 11.9	13.6 13.5	13.4 14.1	70/0 78/0	70/30 78/48	120/50 120/80
P.R.	6:11 yr. 9:11 yr.	3	11.9 11.8	16.1 14.5	16.1 15.0	78/0 92/0	80/60 92/40	98/70 100/70
W.B.	6:6 yr. 12:4 yr.	5:10	10.8 10.7	12.1 11.7	12.3 11.9	12/0 20/0	12/5 20/5	80/50 90/50
R.M.	7 mo. 3:1 yr.	2:6	8.1 9.8	10.6 13.6	11.0 13.0	35/10 30/0	32/10 32/12	90/40 92/60
E.P.	4:8 yr. 8:9 yr.	4:1	9.7 9.8	11.8 12.6	11.9 14.5	85/0 80/0	86/30 80/28	84/64 88/63
P.C.	7 wk. 1:7 yr.	1:5	9.8 9.4	11.2 11.2	11.0 11.9	30/0 40/0	30/5 40/18	— —
N.M.	6:11 yr. 12:11 yr.	6	13.2 11.9	14.4 14.0	14.5 14.8	54/0 40/0	55/13 40/12	100/64 100/60
B.F.	1:5 yr. 6:10 yr.	5:5	9.3 12.0	10.8 14.2	12.0 13.4	20/0 20/0	20/6 22/3	100/58 100/60
K.M.	9 mo. 5:6 yr.	5:9	6.8 10.3	10.1 13.2	10.2 13.3	60/0 50/0	60/30 50/28	80/50 80/48
P.B.	7 wk. 3:3 yr.	3:1	7.1 11.1	9.5 12.7	— 12.0	50/0 18/0	52/30 18/10	75/50 75/40

RA = Right atrium. RV = Right ventricle. PA = Pulmonary artery. SA = Systemic artery.

RESULTS

Shunts were not calculated because oxygen consumption was measured in only a few patients. Magnitude of left-to-right flow as judged by step-up in oxygen content from right atrium to right ventricle was virtually unchanged from study to study, except in three patients first catheterized in the early weeks of life; in these there was a significant reduction in step-up. Arterial oxygen saturation was unchanged in all.

The pressure in the pulmonary artery was normal originally in four individuals. There was no change at the later date, the intervals being 2:8, 5:5, 5:10, and 8:4 years.

In the rest of the patients the systolic pressure ranged from 32 to 90 mm. Hg when first determined. Expressed in terms of percentage of systemic systolic pressure, the range was 35 to 100 per cent. In one child identical pulmonary and systemic pressures (32 mm./92 mm.) were found on both occasions, at 7 months and 3:1 years. In three there was a relative rise (2, 7, and 11 per cent).

Using the same standard (ratio of pulmonary to systemic pressure) there was a decrease in pulmonary pressure in ten individuals. In six this was modest—3 to 6 per cent. A marked change was found in four: 15, 20, 42, and 44 per cent. The first patient was 4:8 years of age when the diagnosis was established, and 8:9 years of age when recatheterized. The respective ages of the other three were 2 months, 3 months, and 4 months, and 3:1 years, 22 months, and 2:5 years.

Systemic pressure was measured on neither occasion in two patients. Both were catheterized for the first time at age 7 weeks, and pulmonary systolic pressure was, respectively, 30 and 50 mm. Hg. In one, 18 months later, the pressure had risen to 40 mm. Hg; in the other, 4:7 years later, it had fallen to 22 mm. Hg.

During the interval between catheterizations there was no significant change in the physical findings and no degeneration in so far as historical evidence was concerned. Four patients who appeared normal to parents at the beginning of the period of observation were similarly situated months or years later. All had normal pulmonary pressure.

Six with signs noted by the parents prior to the first catheterization (easy fatigue, shortness of breath, profuse perspiration, or combinations of these) were neither worse nor better at the time of the second. Initially, these had elevation of pulmonary systolic pressure of 35 to 100 per cent of systemic. In two there was no change in pressure; one showed a rise (11 per cent) and the rest showed a fall (5, 5, and 15 per cent).

The condition of ten of this group was improved. Four had been in obvious cardiac failure when first seen. The initial catheterization followed digitalization and disappearance of all signs of decompensation. Up to the time when the study was repeated, 2:11 to 4:7 years later, there had been no recurrence of failure. Two of these children tired somewhat more quickly than their fellows but were very active; one was asymptomatic and the other appeared normal to the parents except for profuse perspiration. Pulmonary pressure had decreased slightly in two and significantly in one; it had become somewhat higher in one.

Improvement in the remaining six was gauged by a reported increase in exercise tolerance. Pulmonary pressure had been somewhat reduced in four

(interval of 19 months to 6 years), and increased in one (interval of 3:1 years). In the last patient, in whom systemic pressure was not recorded, there was a slight rise in pulmonic systolic pressure—from 30 to 40 mm. Hg—over a period of 18 months.

There was no significant change in the x-rays from study to study. Pulmonary vascular markings were increased in all when the diagnosis of ventricular septal defect was established; their appearance was the same subsequently. The cardiac mass was not appreciably altered, and specific chamber enlargement was as difficult to determine as formerly.

The electrocardiogram was significantly changed in only two patients. There was a significant reduction in amplitude of the R wave in the right precordial leads in an infant in whom the pulmonary systolic pressure was 60 mm. Hg at 3 months of age, and in whom it was 29 mm. Hg 19 months later. A child at 6:11 years had a pattern of right ventricular hypertrophy and a pulmonary systolic pressure of 78 mm. Hg; at 9:11 years, after a 7 per cent increase in pulmonary pressure, as compared to systemic pressure, there was both right and left ventricular hypertrophy.

DISCUSSION

The respect accorded ventricular septal defect has grown exceedingly during the past few years. With the widespread employment of right heart catheterization as a diagnostic tool and the recognition of the malformation as of hemodynamic importance, particularly with regard to the development of pulmonary hypertension, it has come to be accepted as a particularly severe lesion. Indeed, perhaps more than any other cardiac defect, it led to the determined effort to produce a pump-oxygenator which would allow open-heart surgery.

The successful application of open-heart techniques in treating the defect has led to the development of a sense of urgency in submitting patients to surgery. Because those with marked pulmonary hypertension so frequently do not survive operation and those with normal or moderately elevated pressure have fared so much better, surgery in the latter group is insisted upon, the argument being that there will be inevitable progression of pulmonary vascular changes and rise in pressure within a brief period.

The data accumulated in the present series, small as it is, tend to prove that pulmonary vascular resistance, as measured by pulmonary pressure, changes not at all in the majority of patients, at least over a period of some years. A rise is rare. In some infants there is a significant fall.

The clinical information gained from the group indicates that in the period considered there is no obvious deterioration in so far as physical signs or symptomatology are concerned. This has been true, too, in a great many with the defect who have not been recatheterized but have been periodically examined over a number of years. Some individuals, indeed, exhibit appreciable improvement.

One observation which has led to pessimism concerning the outlook of patients with the anomaly is the fact that, although it is the most common of heart malformations in the young, it is seldom found in adults, indicating that

its victims rarely survive to adult years. This was undoubtedly true of past generations. However, it is also true that in the past children with this and other cardiac anomalies were not treated by proper medical measures and had no chance to survive. It is probable that the four in this series who were in failure prior to the first catheterization and who are now progressing satisfactorily would in earlier decades have died because of inadequate therapy. One may assume, with reason, that proper medical management alone will insure the existence of a significantly large adult population with ventricular septal defect in the future.

This study is not presented to minimize the importance of ventricular septal defect. It remains the foremost problem in the field of pediatric cardiology. Rather, the intent is to call attention to the possibility that the current attitude toward its handling is unwise.

The present mortality of open-heart correction is far from negligible. Even in those with normal or moderately elevated pulmonary pressure a respectable percentage fails to survive. Because there is little or no measureable adverse physiologic change in either group in a period of at least a few years after the diagnosis is established, it would seem to be to the best interest of the patients to be wary in electing operation. Time will undoubtedly bring about improvement in surgical technique and probably solve some of the nontechnical problems which now contribute to mortality. Thus, some patients dying as a result of operation now would, if not operated upon, be alive and still operable in the future when their chance of survival would be greater.

It would appear that at the moment the logical candidate for operation is the patient whose pulmonary pressure has been demonstrated by serial catheterization to be rising. Without correction now the risk might soon become inordinate. Moreover, a child who is in failure when first seen and who does not respond to medical measures must also be considered for operation, although obviously a poor risk. Salvage of some is possible.

SUMMARY

Repeat right heart catheterization was carried out in 20 patients from 17 months to 9 years following the initial study.

In only a few patients was there an increase in pulmonary pressure. In some infants there was a significant fall. No deterioration in clinical signs or symptoms occurred.

In view of these data it is suggested that one be wary of electing open-heart operation for the average patient newly discovered to have a ventricular septal defect.

Clinical Experiences With Digoxin†

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Withering, almost 200 years ago, recognized foxglove as the active ingredient in the secret concoction used by a Shropshire woman to dissipate dropsy. For almost 100 years this herb was the only medicament which successfully combated chronic congestive cardiac failure. During the past few decades, physicians and chemists have succeeded in isolating the active ingredients in Withering's herb and also in many other digitalis-like substances. Fortunately for the practitioner, all of these substances have the same salutary and toxic effects on the heart. For this reason, it is usually stated that a physician needs to become familiar with but one substance for each route of administration in order to use digitalis effectively.

All evidence supports the belief that the fundamental cardiac effects of all these substances are identical. It appears fruitless to attempt to determine differences in the toxic to therapeutic ratio of one preparation over another. The increment in dosage of digitalis is too large to detect slight differences, if present, in the effects of these various preparations, particularly because the cardiac and metabolic status varies too much not only from person to person but even in the same person from time to time.

There are, however, reasons for preferring one preparation over another. Stability is an important attribute and represents the major reason that tincture of digitalis has fallen into disuse. There is also the universal tendency to prefer a pure chemical substance to a crude one. Such a substance insures precise dosage, and its effect is compatible with exacting experimental results.

From a clinical standpoint, it would be desirable to have a stable pure substance which can be used intravenously when rapid effect is urgently needed, intramuscularly when oral medication is impossible or inadvisable, and yet is effective orally both for digitalization and for maintenance. A versatile substance of this sort would obviate the need for becoming familiar with any other digitalis preparation. Constant experience would give each physician a more thorough knowledge of its properties.

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†Digoxin was supplied as Lanoxin Injection and Lanoxin Tablets by Burroughs, Wellcome & Co., Inc., Tuckahoe, N. Y.

It is desirable that such a versatile preparation should have two other qualities, a high gastrointestinal to cardiac toxicity ratio and a short duration of toxicity. The first would insure the presence of a symptom which would warn the patient of the possible onset of overdosage. The second is particularly important because toxicity can be produced without change in dosage of digitalis by changes in the patient's metabolic or electrolyte status. It is under these circumstances that gastrointestinal symptoms are usually absent, so that the patient may be first seen in advanced cardiac toxicity sufficient in itself to produce cardiac insufficiency. Life may then depend upon how quickly toxicity disappears or can be overcome.

Digoxin appears to have all these desirable qualities. It is a pure crystalline glycoside isolated by Smith[1] from *Digitalis lanata*. It is said to be effective intravenously, intramuscularly, and orally. It has a high gastrointestinal to cardiac ratio of toxicity. It is rapidly dissipated, thereby insuring a short duration of toxicity. At the same time, it is said to be capable of maintaining digitalization by a daily dose. The pharmacologic characteristics of this drug have been carefully documented by Wayne,[2] Rose, Batterman and DeGraff,[3] and Gold and his associates.[4]

The purpose of this study was to determine the effectiveness, safety, and versatility of digoxin both in restoring and maintaining cardiac compensation in hospitalized and ambulatory patients.

RESULTS

Parenteral Digitalization.—The effectiveness of intravenous administration for emergency use was determined in 6 patients in acute congestive failure with atrial fibrillation (Table I). Lanoxin Injection, 1.5 mg., was given slowly intravenously over a period of 5 minutes. This dose satisfactorily controlled within 2 hours the ventricular rate of the 4 patients with slowly progressive cardiac failure. A single daily oral dose of 0.5 mg. was sufficient to maintain this rate without toxic symptoms or signs. Although the fifth patient maintained a tachycardia, she appeared so much better clinically that no additional digoxin was given that day. On the following day the ventricular rate remained in the low nineties, but because the clinical status was satisfactory, 0.5 mg. was given as a daily maintenance dose. She was discharged on this dose 3 weeks later with a ventricular rate of between 70 and 80 a minute. The sixth patient had multiple pulmonary infarcts and died 10 days after admission, with the ventricular rate uncontrolled even after increasing the daily dose to toxicity (1 mg. on the third day).

To determine the effectiveness of digitalization by the intramuscular route, 1.5 mg. Lanoxin Injection was administered to 3 patients with acute congestive cardiac failure and atrial fibrillation. The speed of action of digoxin intramuscularly was not so rapid as that obtained by the intravenous route. However, a satisfactory fall in the ventricular rate was obtained within 4 hours (Table II).

The usefulness of digoxin intramuscularly was determined in 9 patients, 6 men and 3 women, 37 to 58 years of age, who abruptly developed cardiac failure, although presumably adequately digitalized and maintained (Table III).

TABLE I. THE EFFECT OF INTRAVENOUS INJECTION OF 1.5 MG. DIGOXIN

SUBJECT	AGE (YR.)	SEX	DIAGNOSIS	VENTRICULAR RATE				REACTION	MAINTENANCE (MG.)
				BEFORE DIGITALIZATION	HOURS AFTER DIGITALIZATION				
					1	2	24		
1. M.H.	34	F	Mitral stenosis	138	80	76	84	None	0.5
2. T.J.	46	M	Mitral stenosis	112	74	68	80	None	0.5
3. M.H.	54	M	Hypertension	126	68	58	76	None	0.5
4. F.S.	68	M	Coronary artery disease	118	88	82	84	None	0.5
5. R.D.	63	F	Aortic regurgitation; pulmonary edema	142	98	102	88	None	0.5
6. W.T.	28	M	Mitral stenosis	138	150	144	136	None	Died

TABLE II. THE EFFECT OF INTRAMUSCULAR INJECTION OF 1.5 MG. DIGOXIN

SUBJECT	AGE (YR.)	SEX	DIAGNOSIS	VENTRICULAR RATE			REACTION	MAINTENANCE (MG.)
				BEFORE DIGITALIZATION	HOURS AFTER DIGITALIZATION			
					4	24		
1. G.S.	63	F	Mitral stenosis	126	96	92	None	0.5
2. S.H.	43	F	Mitral stenosis	118	84	88	None	0.5
3. F.H.	47	M	Mitral stenosis	120	86	78	None	0.5

TABLE III. THE EFFECT OF 0.75 MG. DIGOXIN INTRAMUSCULARLY IN 9 PREVIOUSLY DIGITALIZED PATIENTS IN ACUTE HEART FAILURE

DIAGNOSIS	ASSOCIATED ILLNESS	VENTRICULAR RATE			REACTION	MAINTENANCE (MG.)
		BEFORE DIGITALIZATION	HOURS AFTER DIGITALIZATION			
			4	24		
Mitral stenosis	Pulmonary infarction (3) Pneumonitis (3)	132–112	88–102	90–106	None	0.5
Hypertension	Atrial fibrillation (2)	142–136	68–96	78–94	None	0.5
Coronary artery disease	(?)	128	68	64	Premature beats	0.5

TABLE IV. THE EFFECT OF ORAL INGESTION OF 2 MG. DIGOXIN

DIAGNOSIS	NUMBER OF PATIENTS	VENTRICULAR RATE				REACTION	MAINTENANCE (MG.)
		BEFORE DIGITALIZATION	HOURS AFTER DIGITALIZATION				
			1	6	24		
Rheumatic heart disease	18	148–102	94–130	68–92	56–84	Nausea (2)	0.25(2) 0.5(16)
Hypertension	8	126–88	90–110	84–96	74–84	None	0.5
Coronary artery disease	12	132–92	84–106	68–88	76–82	Nausea (1)	0.25(3) 0.5(9)
Pulmonary edema	2	146–110	102–128	82–94	84–88	None	0.5

Six of these patients had recognizable precipitating causes for this failure, which was undoubtedly a stressful situation superimposed upon the cardiac disease. One patient with coronary artery disease developed premature ventricular contractions, which were quickly controlled by potassium acetate. A single intramuscular injection of 0.75 mg. was administered and adequately controlled the ventricular rate within 24 hours in all patients.

Oral Digitalization.—To determine the effectiveness of oral digitalization with Lanoxin, 2 mg. were given in one dose to 40 hospitalized patients in congestive cardiac failure with atrial fibrillation. There were 23 men and 17 women, 28 to 77 years of age (Table IV). We decided to use as the most probable oral digitalization dose 2 mg. of digoxin, because in our experiments with acetyl strophanthidin[5] we found that this dose made a person with heart failure, precipitated by withdrawal of digitalis, intolerant of 0.6 mg. of acetyl strophanthidin. This amount was used as an initial oral digitalizing dose in all persons with failure except those with acute myocardial infarction. We were gratified to find that 2 mg. digoxin produced a satisfactory fall in ventricular rate in all of our patients.

It is important to note that all of these patients were chosen particularly because their failure had been slowly progressive and of a chronic nature. Rapidly developing cardiac failure is usually due to an underlying precipitating factor. It is perhaps for this reason that persons so affected may not respond to digitalis with a similar fall in ventricular rate. In situations of this sort, if the clinical condition appears improved, even though the ventricular rate has not dropped satisfactorily, it is, in our opinion, better to assume temporarily that further improvement will occur with a maintenance dose, because the precipitating cause will be gradually dissipated by additional therapy or will dissipate of itself. If, however, the clinical condition does not appear improved, 0.25 mg. may be added every 6 hours orally or every 2 to 4 hours intravenously until improvement is seen or toxic effects appear. Under all other conditions no further digoxin was given that day and the maintenance dose was begun on the following day.

Maintenance.—To determine the effectiveness of digoxin in maintaining compensation, as well as to learn the optimal maintenance dose, 0.5 mg. was given orally 24 hours after the administration of an initial dose of 2 mg. orally or 1.5 mg. intravenously. If nausea occurred following the first maintenance dose, no more digoxin was given until this symptom disappeared. Then the maintenance dose was started again at 0.25 mg., and increased to 0.5 mg. if the ventricular rate was regarded as too high for the clinical illness. Similarly, if the ventricular rate was too high 6 hours after the initial dose of 0.5 mg., a dose of 0.25 mg. was given every 6 hours until the ventricular response was regarded as satisfactory. Then a maintenance dose of 0.5 mg. was given again, and if necessary was raised to 0.75 mg. At times, the daily maintenance dose was given in two divided amounts 12 hours apart.

In the 40 ambulatory patients the daily maintenance dose varied from 0.25 to 0.75 mg. (Table V). Most commonly, the largest dose was necessary in the rheumatic patients and smallest in the coronary patients. The optimal maintenance dose in the 40 hospitalized patients was 0.5 mg., except for 5 patients.

On this dose, 3 patients, two rheumatic and one coronary, developed nausea and 2 other coronary patients developed a heart rate below 50 a minute. However, these 5 patients were maintained satisfactorily on 0.25 mg. digoxin a day.

TABLE V. ORAL MAINTENANCE DOSE OF DIGOXIN IN 40 AMBULATORY PATIENTS

DIAGNOSIS	DOSE (MG.)			TOTAL NUMBER OF PATIENTS
	0.25	0.50	0.75	
Rheumatic heart disease	3	4	11	18
Hypertension	0	4	0	4
Coronary artery disease	10	6	2	18

It is noteworthy that in many instances after the ventricular rate had been stabilized, the daily dose for the hospitalized patients could be reduced from 0.5 to 0.25 mg. without any significant rise in the ventricular rate. We preferred, however, because of our experiences with our ambulatory patients, to keep our patients on 0.5 mg. a day unless nausea occurred. The reason for the occasionally higher average maintenance dose for the ambulatory patients as compared to that for the hospital patients is easy to understand. Physical activity is a stress upon the heart which tends to raise the heart rate and may tend to require more digitalis for control. Thus we found that the ventricular rate was frequently satisfactory at rest when 0.25 mg. or 0.5 mg. was given, but that simple setting-up exercises at times produced an inordinate rise in the ventricular rate which required an increase in digitalis to prevent it. In many of our rheumatic patients only 0.75 mg. was adequate to control the ventricular rate during normal physical activity or after setting-up exercises.

TABLE VI. THE EFFECT OF SUBSTITUTING AN IDENTICAL INTRAMUSCULAR DOSE FOR AN ORAL DOSE OF DIGOXIN

SUBJECT	AGE (YR.)	SEX	DIAGNOSIS*	VENTRICULAR RATE		REACTION
				BEFORE	5 DAYS LATER	
1. M.L.	64	F	RHD	68	68	None
2. J.McG.	76	F	Cor.	66	68	Nausea 1 day
3. F.K.	60	F	Cor.	80	84	None
4. P.P.	66	F	Cor.	74	78	None
5. A.D.	87	F	Cor.	66	78	None
6. M.M.	77	F	Cor.	72	68	None
7. A.L.	74	F	Cor.	104	88	None
8. M.E.	41	F	RHD	84	60	None
9. E.S.	72	F	RHD, Cor.	77	76	None
10. M.B.	67	F	RHD	86	88	None
11. A.S.	83	F	Cor. Hyp.	68	52	None
12. M.D.	65	F	Hyp.	88	84	None

*RHD = Rheumatic heart disease. Cor. = Coronary artery disease. Hyp. = Hypertension.

The effectiveness of maintenance by intramuscular administration was determined in 12 hospitalized patients by substituting for the oral dose an identical intramuscular dose for 5 consecutive days (Table VI). There are many times when oral medication cannot be given or tolerated, particularly in hospitalized patients and especially postoperatively. Our studies clearly indicate that an intramuscular maintenance dose identical to the oral one is entirely satisfactory. No significant change in ventricular rate occurred nor did toxic symptoms and signs appear.

It was decided to study the feasibility of prolonged maintenance with digoxin. Since digoxin is quite rapidly dissipated as compared to digitalis leaf and digitoxin, many physicians have the mistaken belief that maintenance is difficult with the drug and that compensation will be lost if the daily dose is occasionally omitted. Forty ambulatory cardiac patients were transferred from maintenance with other digitalis preparations to a maintenance dose of digoxin. They were observed weekly for a period of 4 weeks. No difficulty was encountered in maintaining compensation in these patients with a dose of from 0.25 to 0.75 mg. even if an occasional daily dose was omitted. However, an omission of three consecutive daily maintenance doses of digoxin may precipitate cardiac failure in those patients requiring digitalis for compensation.

Toxic Manifestations.—Nausea was almost always the initial manifestation of toxicity with digoxin, and represents one of the most important evidences of the drug's toxic properties. It quickly warns the patient that he has had too much of the glycoside. We always instruct our patients to withhold the digoxin should such nausea appear, and to resume use of the drug once the nausea disappears. If nausea reappears, then the dose is reduced. In only 4 of our ambulatory patients and in none of our hospitalized patients did we recognize the possibility of any form of cardiotoxicity in the absence of nausea. In these 4 patients, premature ventricular beats occurred; all 4 had coronary artery disease. In no instance did any other arrhythmia or any significant block occur. The premature beats were quickly controlled by a diminution in the dose of digoxin.

Not infrequently, the patients who were given large maintenance doses developed nausea. Nausea usually occurred within 30 minutes after ingestion of the drug, and disappeared frequently within an equal length of time. Such rapid appearance of nausea with such quick dissipation suggests that the nausea is probably produced by local action on the stomach rather than by overdigitalization. It is, of course, possible that rapid absorption and rapid dissipation can also account both for the rapid onset and short duration of nausea. This explanation seems unlikely because a smaller dose frequently fails to maintain compensation. Furthermore, under such circumstances we found that nausea could be prevented by giving the digoxin in divided doses. If the daily dose was 0.75 mg., we then prescribed 0.5 mg. in the morning and 0.25 mg. in the evening. If the daily dose was 0.5 mg., this amount was given in two equally divided doses, morning and evening. This type of nausea is to be clearly differentiated from the nausea due to systemic toxicity by the drug. Under such circumstances, nausea usually does not occur until much later or, of course, may be continuous

with the nausea due to local irritation. Furthermore, the nausea usually persists throughout the day, and if the same maintenance dose is continued, the nausea will be continuous.

Further experience with this drug not included in the patients herein reported indicates that serious cardiotoxicity in the absence of nausea may indeed occur as it occurs with other forms of digitalis. But, in our experience, cardiotoxicity in the absence of gastrointestinal manifestations occurs with digoxin only when there are significant metabolic disturbances, particularly depletion of potassium. It is particularly in these circumstances that the short duration of toxicity due to digoxin may be lifesaving.

DISCUSSION

The primary purpose of digitalis is to restore and maintain compensation. Its ultimate effectiveness is readily determinable. Its immediate effectiveness is more difficult, if not impossible, to determine, because restoration of compensation is a time-consuming process which depends not only on the amount of digitalis used and other treatment but also upon the underlying cardiac disease, intensity of cardiac failure, precipitating causes of failure, and many other factors. Most commonly, two methods have been suggested for determining the immediate digitalization dose. One method is to use the smallest amount of the drug that produces toxic symptoms. Such a method requires either one large dose or, more often, repeated doses of digitalis given at very frequent intervals. This method is unpleasant for, and potentially dangerous to, the patient. The other method is to seek a therapeutic effect which can be quantitative on clinical grounds. The most commonly used therapeutic effect is a satisfactory fall in the ventricular rate of persons with atrial fibrillation and a fast ventricular rate.

Satisfactory fall in ventricular rate is a vague term. Most often one speaks of a fall in ventricular rate to normal, but this effect is obviously impossible (without toxicity) in many clinical illnesses. Fever, thyrotoxicosis, high-grade valvular lesions, acute myocardial infarctions, pulmonary infarction, and many other abnormalities raise the ventricular rate in the absence of cardiac failure. For this reason we prefer to speak of a fall in ventricular rate as one which was anticipated had failure not been present. A drop in, or complete disappearance of, a pulse deficit is usually associated with this fall.

We chose as our probable oral digitalization dose the amount of digoxin which made a person with heart failure, precipitated by withdrawal of digitalis, intolerant of 0.6 mg. of acetyl strophanthidin.[5]

On the many occasions when oral medication cannot be given or tolerated, particularly in hospitalized patients and especially postoperatively, we have found that digoxin intramuscularly may be used effectively for digitalizing as well as for maintaining patients. This method is indeed the preferred one if oral digitalization is not possible. Only in emergencies should the intravenous route be used. One such emergency may be failure due to myocardial infarction. Patients with this illness are very intolerant of the average digitalization and maintenance dose of digitalis. In such dire emergencies, therefore, it is our

practice to give initially no more than one half of the oral dose, both for digitalization and for maintenance.

The subject of maintenance with digitalis calls for some discussion. From a pharmacologic point of view, it can be demonstrated that the effect of digitalis outlasts its actual presence in the body. It is often difficult to realize that the concentration of the drug necessary to maintain full effects is less than that required to initiate these effects. It has been demonstrated by Gold,[4] Wayne,[2] and DeGraff[3] that if one gives a single dose of 1 to 2 mg. digoxin to a patient in congestive heart failure following the restoration of compensation, an average of 4 to 5 days elapses before the patient again develops decompensation. If such a patient, from whom digoxin has been withheld, is placed upon a maintenance dose for a day or two before congestive failure returns, decompensation will not occur even though the digoxin has been almost completely dissipated. The major problems in maintenance are the achievement of satisfactory initial digitalization and the administration of an adequate daily dose. This implies that each patient is an individual with respect to dosage. Individualization is usually begun 24 hours after the initial priming (probable digitalization) dose. Only in the more urgent instances is it begun 6 hours after the priming dose.

SUMMARY

1. These results indicate that Lanoxin is a safe, effective, and versatile preparation for oral, intramuscular, and intravenous use.

2. A safe initial digitalizing dose appears to be either 2 mg. orally or 1.5 mg. intravenously or intramuscularly, unless acute myocardial infarction is present or suspected. Under such circumstances one half of each of these doses is used.

3. A dose of 0.75 mg. intramuscularly is safe and usually effective for those who, previously well maintained, fail abruptly because of a precipitating event.

4. Individualization of dosage is started 24 hours after the initial dose. If the fall in ventricular rate is satisfactory, and nausea is absent, the patient is placed on a maintenance dose of 0.5 mg. If nausea is present, which is extremely rare, no further digoxin is given until this symptom disappears. A maintenance dose of 0.25 mg. is then started, and is increased to 0.5 mg. if the ventricular rate is regarded as too high for the clinical illness. If the ventricular rate and pulse deficit have not been corrected satisfactorily, 0.25 mg. is given every 6 hours until such a response occurs or toxic symptoms appear before starting the maintenance dose.

5. Only in obviously urgent circumstances is individualization of dosage begun 6 hours after the initial dose.

6. The average maintenance dose of digoxin is 0.25 to 0.75 mg. No difficulty was encountered in maintaining patients on digoxin in spite of its fairly rapid dissipation. Although there is considerable overlapping, the coronary patients usually require the smallest dose, the rheumatic patients the largest dose, and the hypertensive patients a mean of the two.

7. An intramuscular maintenance dose of digoxin identical to the oral dose may be substituted without any noticeable change in the drug's effectiveness.

8. Nausea is almost always the initial manifestation of toxicity with digoxin. Only when severe depletion of potassium is present may cardiotoxic effects occur in the absence of gastrointestinal symptoms.

9. It is necessary to differentiate a systemic from a local emetic action of digitalis. Time may often be used as a deciding factor to make this distinction. We considered instances in which nausea occurred within 30 minutes of ingestion of the drug and was of short duration to be due to local gastric distress. Under such circumstances, giving the total maintenance dose in two equal amounts, morning and evening, corrected the situation.

We are grateful to Dr. William Winters, Jr., Fellow in Cardiology, for collecting some of the data on ambulatory patients.

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Isolated Infundibular Stenosis

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Some observers have said that isolated infundibular stenosis (subvalvular pulmonic stenosis with intact ventricular septum) is not an uncommon congenital heart lesion, while others have considered it to be a very rare congenital lesion.

Paul Wood[1] stated that in a series of 750 cases of congenital heart disease 2 per cent, or 15 patients, had isolated infundibular stenosis. He also stated that 4 out of 5 of all cases of pure pulmonic stenosis are valvular, and that 1 out of 5 is infundibular.[2] On the other hand, Maurice Campbell[3] found only 2 cases of isolated infundibular stenosis in his series of 1,130 cases of congenital heart disease, of which 113 were cases of pure pulmonic stenosis, and only one of those two cases was confirmed by surgery. Maude Abbott[4] reported only 2 cases of infundibular stenosis with closed interventricular septum in her 1,000 autopsied cases of congenital heart disease.

We report here 3 cases of well-documented infundibular stenosis, with the pre- and postoperative catheterization data, and discuss the relative frequency, clinical manifestations, and results of surgical correction of this lesion.

CASE REPORTS

CASE 1.—J. W., a 21-year-old white woman, was first seen at our clinic in December, 1956. She had had a known heart murmur since shortly after birth, but she got along well until June, 1956, when she developed chills and fever; at this time a diagnosis of rheumatic fever was considered. Subsequently, the patient complained of fatigue and exhaustion at the end of a day, and her exercise tolerance was no more than walking 1 to 2 blocks. There was no history of cyanosis, edema, coma, convulsions, paroxysmal noctural dyspnea, nor signs and symptoms of congestive heart failure. She had two episodes of syncope. Her physicians were concerned about the definite change in her heart murmur with her recent illness, and referred her to us for diagnosis and possible treatment. Her past history was noncontributory, and the physical examination was entirely normal except for her heart.

Heart.—The precordium was quiet. There was regular sinus rhythm. The heart appeared to be borderline as regards over-all heart size. A systolic thrill was palpable over the entire precordium, and with the patient in the reclining position it was of maximum intensity in the third

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left intercostal space at the sternal border. No shocks were present. There was a rather sustained thrust at the lower left sternal border, suggesting right ventricular hypertrophy. Auscultation revealed a systolic murmur, Grade 6 in intensity, which was readily audible over the olecranon process of the elbow and everywhere over the precordium and chest. This was a very harsh, rasping, obstructive type of murmur and was maximal in the third left intercostal space at the sternal border. Here the murmur could be heard by ear alone, and by ear anywhere from 4 to 6 inches from the chest wall. The murmur completely destroyed the integrity of the first and second pulmonary heart sounds. The murmur was definitely louder in the third left intercostal space than in the first left intercostal space, and was also as loud in the fourth left intercostal space as in the second left intercostal space.

Electrocardiogram.—The electrocardiogram revealed a sinus tachycardia with a rate of 138 per minute and very definite evidence of right ventricular hypertrophy.

Fluoroscopy.—The main pulmonary artery was larger than normal. The right and left pulmonary arteries were of normal size. Increased pulsations were noted over the main pulmonary artery, in contrast to the somewhat lesser amplitude of pulsations over the right and left pulmonary arteries. The over-all heart size was slightly enlarged. The right atrium and right ventricle were both definitely enlarged in all views. The rest of the examination was normal (Fig. 1).

Clinical Impression.—The clinical impression was infundibular stenosis, with the possibility of valvular pulmonic stenosis as well.

Cardiac Catheterization.—Cardiac catheterization was carried out on Dec. 7, 1956 (Table I; Fig. 2). The pulmonary arterial pressure pulses were of low amplitude and markedly damped, indicating stenosis. The mean pulmonary arterial pressure was 9 mm. Hg. As the catheter tip was withdrawn, there was no change in pressure suggesting an infundibular chamber. However, there was an abrupt rise in systolic pressure, not at the usual site of the pulmonic valve but well down into the ventricular shadow. This low point of transition was confirmed by repeated observations. Systolic pressure within the right ventricle varied from 75 to 90 mm. Hg, giving a systolic gradient across the stenosis of about 70 mm. Hg. The right atrial pressure pulse did not show prominent "a" waves. There was no evidence of a shunt in either direction. The catheterization impression was isolated infundibular stenosis.

Surgery.—On Dec. 11, 1956, under hypothermia, the chest was opened. The heart was slightly enlarged. There was a clear-cut infundibular chamber with stenosis about 4 cm. below the level of the pulmonary valve. The systolic thrill was maxmal in the chamber and petered out along the pulmonary artery, which showed only a slight amount of poststenotic dilatation. Upon opening the ventricle, we looked into an infundibular chamber which would have admitted the index finger up to the first joint. The stenotic area was surrounded by a rim of fibrous tissue; in addition, a broad band of muscle comprised its posterior border and extended obliquely upward across the lumen of the ventricle. The procedure consisted in grasping the tissue with a forceps and using the Mayo scissors to excise the fibrous ring and a large piece of the obstructing muscle. At the conclusion of this procedure it would have been easy to place three fingers through the opening. There were no additional areas of stenosis. The pulmonary valve and ventricular septum were examined and appeared to be normal. The entire occlusion time was 5 minutes and 5 seconds. No bright red blood entered the right ventricle during this period.

Postoperative Catheterization.—Postoperative catheterization was performed on July 23, 1957 (Table I; Fig. 2). There was no longer a systolic pressure gradient between the pulmonary artery and the right ventricle. There was no evidence of any shunt being present. A dye dilution curve following injection of Evans blue dye into the superior vena cava was perfectly normal.

Last Postoperative Evaluation.—On July 22, 1957, the patient was 8 months postoperative. She was asymptomatic, and stated that she felt better than she has ever felt in her life. It was impossible to say what her exercise tolerance was because she tended to be most conservative in her activities.

Physical examination revealed that a slight parasternal lift was still present, suggesting right ventricular hypertrophy. No thrill was palpable. There was a Grade 2 to 3 systolic murmur of maximum intensity in the second left intercostal space. It was rough but no longer harsh nor rasping in character. The pulmonic second sound was of good intensity and definitely split.

TABLE I. PRE- AND POSTOPERATIVE CATHETERIZATION

	OXYGEN SATURATION (IN PER CENT)							
	S.V.C.	I.V.C.	R.A.	R.V.	M.P.A.	B.A.	P.A. (EXERCISE)	B.A. (EXERCISE)
J. W. Preop.	62.4	——	66.5	68.9	66.7	95.2	——	——
Postop.	72.7	61.3	69.5	69.8	71.0	91.0	——	——
D. S. Preop.	69.8	72.7	70.7	71.5	69.1	95.5	49.1	94.4
Postop.	65.3	69.4	67.0	67.0	68.0	94.9	41.6	87.1
L. H. Preop.	54.1	44.6	48.2	45.8	50.8	97.3	35.9	89.8
Postop.	71.5	72.9	68.2	69.4	73.6	92.7	59.3	93.6

	PRESSURES (IN MM. Hg)								
	R.A.	R.V.	INF.	M.P.A.	WEDGE	B.A.	P.A. (EXERCISE)	B.A. (EXERCISE)	R.V. (EXERCISE)
J. W. Preop.	5/4	—	—	12/7	7/5	130/80	—	—	—
Postop.	8/5	22/2	—	22/14	15/10	138/72	—	—	—
D. S. Preop.	13/7	100/–3/12	—	25/10	8/6	133/65	—	180/92	—
Postop.	13/7	58/11	—	22/8	—	138/72	25/10	175/80	93/3
L. H. Preop.	15/6	145/–3/10	28/2	28/12	11/7	105/65	51/33	118/86	—
Postop.	11/7	50/–5/10	—	50/18	—	110/72	—	—	—

	CARDIAC INDEX (IN L./MIN./M.^{2})	CARDIAC INDEX AT REST	CARDIAC INDEX DURING EXERCISE
J. W. Preop.		2.2	—
Postop.		3.4	—
D. S. Preop.		2.6	5.3
Postop.		3.71	5.5
L. H. Preop.		3.6	4.7
Postop.		4.7	5.3

A. *B.* *C.*

Fig. 1.—Preoperative posteroanterior chest x-ray films. *A*, Patient J. W. *B*, Patient D. S. *C*, Patient L. H.

Electrocardiographically, there has been marked regression in the degree of right ventricular hypertrophy as compared with preoperative tracings. However, definite evidence of right ventricular hypertrophy was still present.

On fluoroscopy, the main pulmonary artery continued to be slightly prominent and the right and left pulmonary arteries were of fair size. The amplitude of pulsations was equal over these vessels. The right atrium and right ventricle were still enlarged, and there was a slight increase in the over-all size of the heart as compared to preoperative x-rays.

The clinical impression was that this girl had been completely cured of her disease. She was completely asymptomatic and revealed no pressure gradient across the pulmonic valvular area by cardiac catheterization.

CASE 2.—D. S., a 20-year-old white man, was first seen in our clinic in May, 1954. He was born of a normal full-term pregnancy and delivery. He was noted to be blue at birth, and this condition persisted for 3 days before disappearing. Shortly thereafter it was noted that he had a heart murmur and a "bad heart." Growth and development were normal. At the age of 10 years the patient began experiencing episodes of unconsciousness occurring about twice yearly. These usually occurred on very hot days when the patient was out in the sun. No convulsions nor paralysis accompanied these episodes. He had not experienced syncopal attacks in the last 5 years. The patient denied any serious illnesses, rheumatic fever, chorea, strokes, cough, hemoptysis, or paroxysmal nocturnal dyspnea. He had moderate limitation to strenuous exercise but this had not been progressive. Ever since birth the patient had had a dusky complexion, and the question of cyanosis had been raised many times but never definitely confirmed. He did light work on the farm but he usually slept in the afternoon because his endurance was not up to that of his brothers.

Physical Examination.—The patient was a well-developed, well-nourished, white male with a certain duskiness to his complexion and to his lips and nail beds. Definite central cyanosis was not present.

Heart.—A very prominent "a" wave was noted in the neck. The point of maximal impulse was in the fifth left intercostal space in the mid-clavicular line. A regular sinus rhythm was present. A slight right ventricular lift was noted along the lower left sternal border. A systolic thrill was felt along the left sternal border, most prominently in the second and third left intercostal spaces. On auscultation, the second heart tone at the base was completely obscured by a Grade 4, harsh systolic murmur which was audible all over the precordium, but which was loudest at the second and third left intercostal spaces parasternally. The murmur was louder in the fourth left intercostal space than in the first left intercostal space. The murmur was well heard in the back and in the neck bilaterally. The second heart tone could be heard along the lower left sternal border and at the apex, and seemed to be split.

Electrocardiogram.—The over-all interpretation of the electrocardiogram was right ventricular hypertrophy, but the unusual electrical cardiac position detracted somewhat from the assurance with which this diagnosis was made.

Fluoroscopy.—Enlargement of the right ventricle and the right atrium was noted. There was no prominence in the region of the main pulmonary artery. This area was concave. The left pulmonary artery appeared to be prominent and dilated, while the right pulmonary artery appeared normal. Amplitude of pulsations in the pulmonary artery appeared normal. Peripheral vascularity of the lung fields was normal (Fig. 1).

Clinical Impression.—The clinical impression was infundibular stenosis either alone or with a ventricular septal defect (tetralogy of Fallot).

Cardiac Catheterization.—Cardiac catheterization was carried out on July 20, 1954 (Table I; Fig. 3). There was a well-demonstrated systolic pressure gradient between the pulmonary artery and the right ventricle. No evidence of an infundibular chamber was noted, but the transition zone was not noted at the usual valvular area. It appeared to be down one third of the distance along the left heart border. There was no evidence of a shunt. Peripheral saturations at rest and on exercise were normal. The catheterization impression was isolated infundibular stenosis.

Surgery.—On April 2, 1957, under hypothermia, the chest was opened. The heart appeared enlarged. The right auricle and right ventricle were enlarged. A very small (1 cm.) infundibular

chamber was present. At this point the thrill began, and became maximal distal to this on the pulmonary artery. There was a visible flutter of the artery. The poststenotic dilatation was moderate. The ventricle was opened and a fibrous ring was cut which opened into the little infundibular chamber which was triangular in shape. The obstructing ring almost fused with the valve ring posteriorly, and anteriorly it was 1 cm. below the valve. This tissue was excised. The pulmonary valve appeared normal. The rest of the right ventricle appeared normal. The ventricular septum was examined and no defects were noted. The total occlusion time was 4 minutes and 30 seconds. Again, no bright red blood was noted to enter the right ventricle.

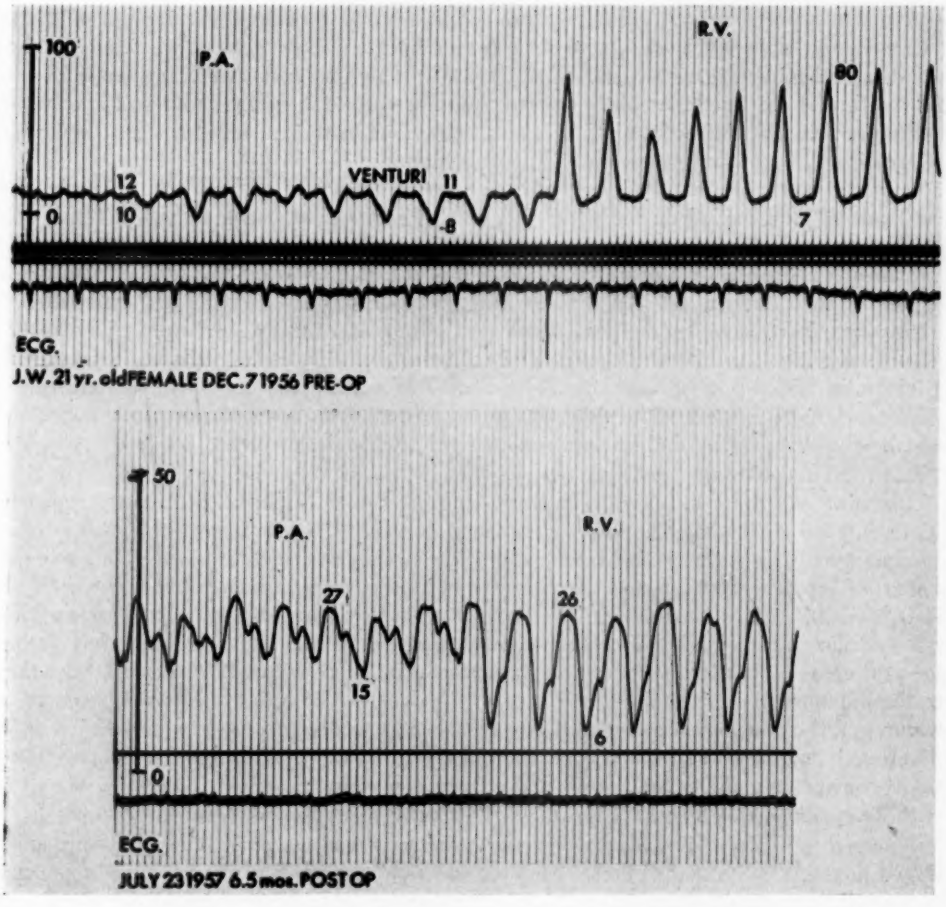

Fig. 2.—Preoperative and postoperative catheter tracings across the pulmonary valve of Patient J. W. Note the Venturi effect on the preoperative tracing. The pressure gradient has been abolished by surgery.

Postoperative Catheterization.—Postoperative catheterization was performed on May 16, 1957 (Table I; Fig. 3). From a pressure of 22/8 mm. Hg in the pulmonary artery, there was a jump to 58/11 as the catheter tip was withdrawn into the right ventricle. This gave a resting systolic gradient of 36 mm. Hg as compared to 75 mm. Hg prior to surgery. During exercise there was a significant increase in this gradient to 68 mm. Hg, with a corresponding right ventricular pressure of 93/3 mm. Hg. The right atrial pulse contour displayed prominent "a" waves. An Evans blue dye curve was obtained, with the dye being injected into the superior vena cava; no right-to-left shunt was demonstrable.

Last Postoperative Evaluation.—The patient felt well and had noted an increase in exercise tolerance. A regular sinus rhythm was present. A right ventricular lift was still present along the lower left sternal border. A Grade 3, harsh, obstructive systolic murmur was heard all over the percordium, but was loudest in the third left intercostal space and louder in the fourth than in the first left intercostal space. The murmur had lost some of its harsh quality. The electrocardiogram was unchanged.

On fluoroscopy, the heart appeared to be somewhat larger than it was before surgery, with the enlargement appearing to be in the right ventricular area. The lung fields showed no change except for some postoperative blunting of the left costophrenic angle.

The clinical impression was that this boy still had a moderate degree of infundibular stenosis present 6 weeks postsurgery. He felt better but had not had complete correction of his lesion.

CASE 3.—L. H., a 9-year-old boy, was first seen by us on Dec. 3, 1955, when he was admitted to this hospital following an automobile accident in which he sustained a basilar skull fracture and a fracture of the left mandible. On admission, a very loud systolic murmur was audible all over the precordium, and because of this and a previous history of fainting spells and cyanosis, the Cardiology Department was called in consultation.

The child had had a known heart murmur since 1½ years of age. At that time he had frequent "passing out spells" during which his entire body would become rigid. These episodes would last about 5 minutes and be accompanied by facial cyanosis. He would continue to have respirations. There were no convulsions and no postictal drowsiness. These episodes recurred infrequently until the age of 5 years, when they completely subsided. He had experienced some effort intolerance marked by dyspnea upon stair climbing, running, and strenuous exercise, and could not keep up with children his own age in this respect. There had been no history of squatting, cyanosis, or paroxysmal nocturnal dyspnea. The past history was noncontributory.

Physical Examination.—The child was found to be below the tenth percentile for height and weight on the Wetzel grid, and he appeared somewhat chronically ill.

Heart.—The point of maximal impulse was in the fifth left intercostal space in the midclavicular line and quite localized. There was no precordial bulge. There was a suggestion of a right ventricular lift along the lower left sternal border. There was a prominent systolic thrill at the base, greatest in the second intercostal space at the left sternal border. This was not well transmitted into the suprasternal notch nor into the carotid vessels. There were no shocks, thrusts, nor abnormal pulsations. A regular sinus rhythm was present. There was a Grade 6, harsh systolic murmur, of the obstructive type, heard loudest at the second left intercostal space at the sternal border. As auscultation was continued down the left sternal border the murmur became more high-pitched and radiated to the apex. The heart tones were obscured by the murmur, and the tones in the second left intercostal space were either greatly diminished or absent. In the fourth left intercostal space the second heart sound was accentuated and pure. The heart tones at the apex were not remarkable.

Electrocardiogram.—The ECG revealed right ventricular hypertrophy.

Fluoroscopy.—Normal to decreased lung vascularity was present. The heart was somewhat enlarged in the transverse diameter. The left and right pulmonary arteries were of normal size, with normal pulsations. The aorta was not remarkable. The main pulmonary artery was prominent, but the pulsations were not unusual. In the oblique views the right ventricle and right atrium were considered to be enlarged. The left ventricle and left atrium were not enlarged (Fig. 1).

Clinical Impression.—The clinical impression was valvular pulmonic stenosis.

Cardiac Catheterization.—Cardiac catheterization was carried out on Jan. 20, 1956 (Table I; Fig. 4). The pulmonary arterial pressure was moderately elevated at rest, being 30/12 mm. Hg, and rose to 51/33 mm. Hg during exercise. Upon withdrawal of the catheter from the pulmonary artery into the right ventricle an infundibular-chamber type of pressure record was obtained. This infundibular-chamber pressure pattern started when the tip of the catheter passed the area of the pulmonary valve and ended rather low in the right ventricle. The right ventricular pressure was markedly elevated at rest, being 145/10/−3 mm. Hg, and the right atrial pressure was slightly elevated, being 15/6 mm. Hg. The peripheral arterial saturation was 97.3 per cent at rest and 89.8 per cent during exercise.

Catheterization Impression.—The catheterization impression was isolated infundibular stenosis with possible right-to-left shunt through a patent foramen ovale during exercise.

Surgery.—On Jan. 24, 1956, under general anesthesia, the patient was cooled to 26.5° C. and the chest opened. The pulmonary artery was of normal size. There was an easily visible infundibular chamber which beat out of phase with the remainder of the ventricle, which, while not remarkably enlarged, was clearly hypertrophied and very thick and stiff. There was a thrill of considerable intensity palpable in the infundibular chamber, and this was transmitted into the various adjacent structures.

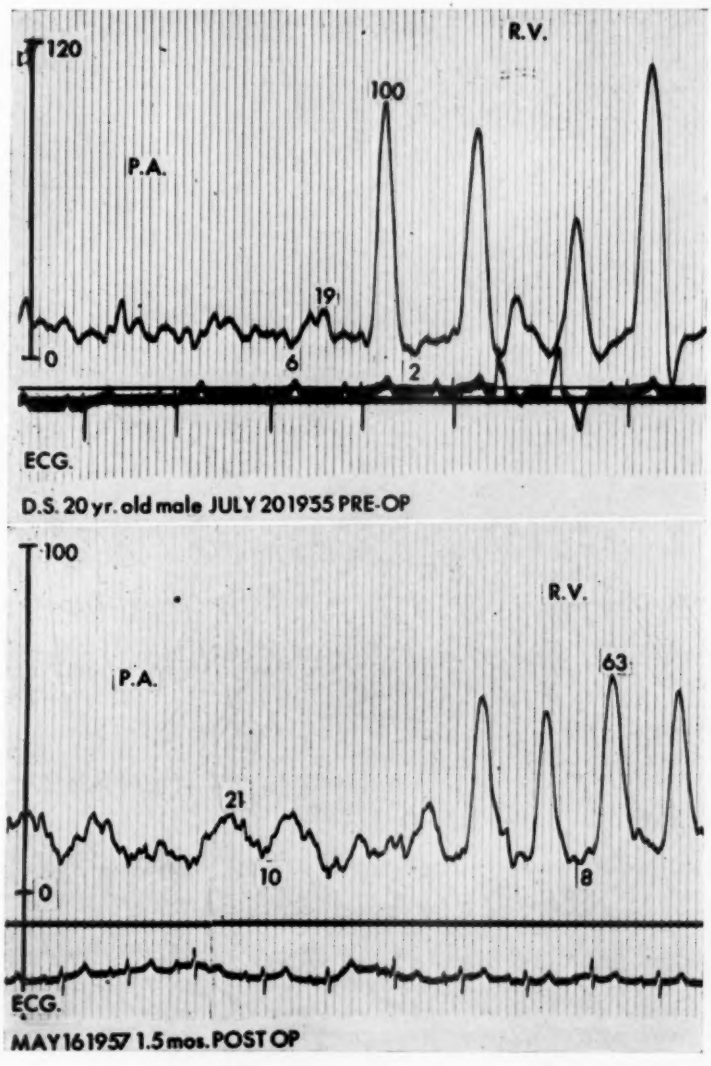

Fig. 3.—Preoperative and postoperative catheter tracings across the pulmonary valve of Patient D. S. Note the absence of an infundibular-chamber pressure tracing preoperatively and the residual stenosis present postoperatively.

An incision in the right ventricle was made and the wall of the infundibular chamber was seen to be about 3 mm. thick. A tight infundibular stenosis could be seen. The lumen would not admit the tip of the little finger and was about 3 mm. in diameter. It was surrounded by a very white fibrous endocardium, which was thickened and firm. The operation consisted

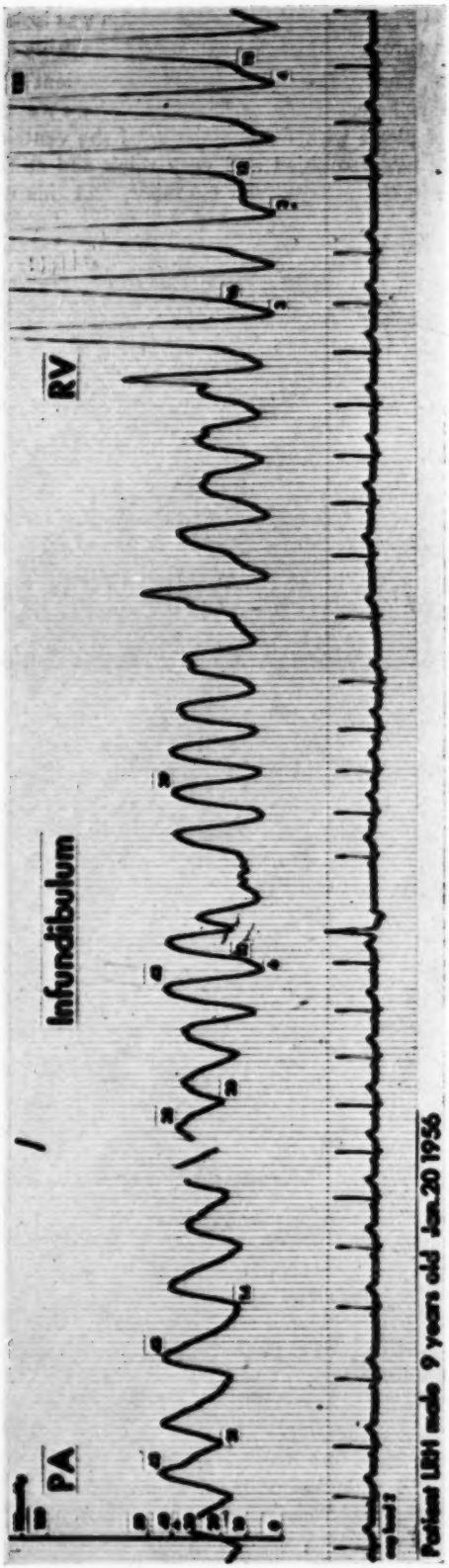

Fig. 4.—*(For legend see opposite page.)*

in excision of tissue in all parts of this infundibular obstruction. First, a large segment of crista was removed; then, the fibrous tissue was excised and, finally, some additional muscle. At last it was possible to pass the index finger into the lumen of the ventricle and to palpate for a high intraventricular septal defect. None was felt. The pulmonary valve itself was normal. No bright red blood was seen to well up in the right ventricle during the procedure. The total occlusion time was 5 minutes and 40 seconds. Following the manipulation of the infundibular area, a thrill could no longer be detected in the infundibular chamber. The child had an uneventful recovery.

Postoperative Catheterization.—Postoperative catheterization was performed on Feb. 15, 1957 (Table I; Fig. 4). There was no longer any systolic pressure gradient between the right ventricle and the pulmonary artery, but definite pulmonary hypertension was present. There was no shunt present. The systemic arterial saturation at rest was 92.7 per cent, and it rose on exercise to 93.6 per cent.

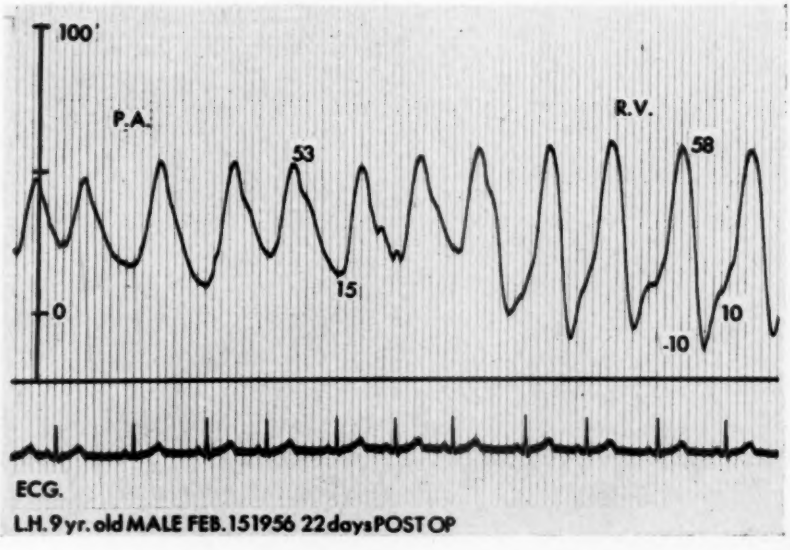

Fig. 4.—Preoperative and postoperative catheter tracings across the pulmonary valve in Patient L. H. Note the infundibular-chamber pressure tracing preoperatively and the complete absence of a pressure gradient postoperatively. The postoperative tracing reveals moderate pulmonary hypertension.

Last Postoperative Evaluation.—One and one-half years postoperatively, on June 11, 1957, the patient was symptomatically much improved. He climbed stairs, ran, and could keep up with his playmates, although he still had a slight impairment of exercise tolerance.

On physical examination, findings pertinent to the heart showed that there was no palpable right ventricular lift. There was a systolic thrust palpable over the pulmonic area, and a shock coincident with the valve closure. There was no increase in precordial activity. There was a Grade 3, moderately rasping, systolic murmur maximal in the third left intercostal space, and greater in the second than in the fourth. The second pulmonic sound was accentuated, was greater than the second aortic sound, and was moderately widely split. There were no other murmurs or thrills present.

Electrocardiographically, the degree of right ventricular hypertrophy was not so great as preoperatively.

On fluoroscopy, the main pulmonary artery was seen to be enlarged. The pulmonary vasculature was normal. There was evidence of right ventricular enlargement.

The clinical impression was that the pressure gradient had been abolished by surgery, but that the patient now had residual pulmonary hypertension of moderate degree.

DISCUSSION

From the first description of pure infundibular stenosis by Elliotson,[5] in 1830, until 1948, when general application of cardiac catheterization came into use, only 14 autopsied cases had been reported. Keith,[6] in his classic lectures on malformations of the heart, alludes to some cases of pure infundibular stenosis, but the cases are not described adequately and we do not know whether any of his cases were previously reported. Since that time, most series of cases of pulmonic stenosis with intact ventricular septum have had a few cases of what are believed to be pure infundibular stenosis. Besides the series of Wood and Campbell, alluded to in the introduction, Kjellberg[7] has reported three out of 25, Dow[8] one out of eight, Glover[9] four out of 25, Joos[10] one out of 26, Abrahams[11] eight out of 69, Dimond[12] two out of 20, Kirklin[13,14] three out of 19. Van Loo and associates[15] reported on six cases of infundibular stenosis, of which four were of the isolated variety. Brock,[16] in a more recent study, states that he has operated upon nine cases of infundibular stenosis as compared to 111 cases of valvular stenosis. In a perusal of the literature since 1948, we found that about 60 cases of isolated infundibular stenosis have been reported. The great majority of these has been diagnosed by catheterization, a small number has been diagnosed at operation, and the fewest number has been diagnosed at autopsy. Certainly there have been other cases confirmed but not reported.

At the University of Colorado Medical Center, we have observed 138 cases of isolated pulmonary stenosis. We have included all patients with valvular and subvalvular stenosis with intact ventricular septa. Of this total number there were 21 patients with right-to-left shunts through a foramen ovale. Patients with pulmonary stenosis and a demonstrable left-to-right shunt through an atrial defect at postoperative catheterization have been excluded from this series. Sixty-eight patients of our series have been operated upon; sixty-five have had valvular stenosis and three have had infundibular stenosis. Forty-six patients have the clinical diagnosis of valvular pulmonic stenosis and have been catheterized. The catheterization confirmed the diagnosis in all of these patients. They have not been operated upon because we have considered the stenosis not to be of sufficient severity to warrant operation. One patient with the clinical diagnosis of infundibular pulmonic stenosis has been catheterized, but his clinical condition and pressure gradient do not warrant surgical intervention at this time. Twenty-three patients with the clinical diagnosis of mild valvular stenosis have not been subjected to catheterization. Our series shows, therefore, four cases of isolated infundibular stenosis out of 138 cases of pulmonary stenosis, or an incidence of 2.9 per cent of all cases of isolated pulmonic stenosis. Of our operated cases of isolated pulmonic stenosis 4.4 per cent are cases of isolated infundibular stenosis.

Pathology.—Infundibular stenosis is caused by arrest of the normal involution of the bulbus cordis, which should be incorporated into the right ventricle by the end of the second month of intrauterine life, forming the infundibulum, conus or outflow tract.[6]

The stenosis may be of two types: (1) There may be a fibrous band at the line of junction of the cavity of the right ventricle and the infundibulum. This

produces a stenosis of the orifice of the infundibulum and divides the right ventricle in two. The infundibulum may be enormously dilated above the constriction. (2) The infundibulum may be shrunken in size, with thick muscular walls constituting a fusiform stenotic outlet to the right ventricle. However, in this type there can be a wide variation in the anatomy of the infundibular stenosis. The obstructed area may be short or long, high in the right ventricle or lower down.[17]

The abnormal position of the crista supraventricularis and, particularly, of its two band-shaped extensions, the septal and parietal bands, causes the different varieties of infundibular stenosis. The bands, which usually run in a distal direction, are displaced forward and upward. The parietal band runs in an arch to the left, whereas the septal band leaves the septum and deviates medially. With severe displacement of the band, the whole infundibulum is compressed into a long, narrow channel. With less severe displacement, the constriction is more circumscribed and is often confined to the orifice of the infundibulum. In the overwhelming majority of cases, infundibular stenosis is associated with an intraventricular septal defect.[6,18] Owing to the displacement of the crista and the parietal band ventrally and to the left, the normal closure of the interventricular foramen is incomplete or fails to occur.

Clinical Evaluation.—

Symptoms: The history that these patients present is indistinguishable from that given by those with valvular stenosis. Those with mild stenosis are invariably asymptomatic. Those with severe stenosis exhibit symptoms which are due to inadequate cardiac output; these are effort dyspnea, angina pectoris, syncope, fatigue, dizziness, and, finally, pedal edema and right-sided congestive failure. Occasionally, patients with severe stenosis may be asymptomatic. Central cyanosis and clubbing of the fingers may be present if the stenosis is severe and a patent foramen ovale is present. Needless to say, all these patients have had heart murmurs present since birth.

Physical and x-ray findings: All patients have a loud (Grade 3-4) systolic murmur heard along the left sternal border, and the great majority has a concomitant thrill. There are numerous findings described in the literature designed to differentiate valvular from infundibular stenosis on physical examination and x-ray.

Some of the findings described in infundibular stenosis are the following: (1) There may be no right ventricular parasternal lift if the stenosis is exceptionally low. (2) The thrill and the maximum intensity of the systolic murmur is lower, usually in the third left intercostal space parasternally.[19] (3) The murmur begins immediately after the first sound, diminishes in late systole, and ends with the aortic component of the second sound. (4) Both components of the second sound are audible, the pulmonary sound usually being fainter than the aortic, and the split is quite wide.[20] (5) The poststenotic dilatation of the main pulmonary artery on x-ray is usually absent. (6) In the right anterior oblique view there is usually a bulging of the lower left mid-segment. (7) The prominent pulsations of the main pulmonary artery with normal or decreased pulsations of the right or left pulmonary artery are usually not seen.

All three of our patients reported in this paper had a left parasternal lift, but it was noted to be slight in all. The maximum intensity of the murmur and thrill were consistently lower than in valvular stenosis. They were most intense in the second to third left intercostal spaces parasternally and tended to be more rasping in quality than in valvular stenosis. No diastolic murmurs were heard in any of the cases. In only one case was the second sound split. In no case was a bulging of the left lower mid-segment seen. In one of the cases prominent pulsations were seen in the main pulmonary artery, with decreased pulsations in the right and left pulmonary arteries.

The correlation between fluoroscopic and x-ray evidence of the presence or absence of the poststenotic dilatation of the pulmonary artery and the actual amount of dilatation visible at surgery showed agreement in only one case out of three. On the other hand, Case 1 showed an apparent poststenotic dilatation by x-ray but very little at surgery, while Case 2 showed no poststenotic dilatation on x-ray but a moderate amount at surgery.

Therefore, on physical examination and routine cardiac x-rays the only consistent finding was that the maximum intensity of the systolic murmur and thrill was in the second to third left intercostal spaces parasternally, which is lower than the murmur and thrill of valvular stenosis. In no case was the murmur louder in the first left intercostal space than it was in the third. The murmur is considered to be more rasping in quality in the case of infundibular stenosis.

If our patients be representative, it seems that there has been no valid advance in our ability to clinically differentiate isolated valvular from infundibular stenosis since Barié, in 1895, noted that the murmur and thrill were consistently lower in infundibular stenosis.

Electrocardiogram: The electrocardiogram reveals right ventricular hypertrophy in most cases of moderate stenosis and in all cases of severe stenosis. In general, the severity of the stenosis varies directly with the degree of right ventricular hypertrophy noted in the electrocardiogram. In view of the large right atrium present in all cases on fluoroscopy, one would expect to see evidence of right atrial enlargement on the electrocardiogram, but in none of our cases was this true.

Ancillary Diagnostic Procedures.—

Cardiac catheterization: It has been postulated that cardiac catheterization can establish the diagnosis of infundibular stenosis by revealing three distinct pressure zones in pulling back from the pulmonary artery to the right ventricle, the lowest mean pressure being in the infundibulum.[11] In going from the pulmonary artery through the valve into the infundibulum, the systolic pressure is fairly constant, unless valvular stenosis is present also, but the diastolic pressure drops. As the catheter passes from the infundibular chamber into the right ventricle, the systolic pressure is markedly elevated and the diastolic pressure remains constant. In addition, the right ventricular pressure curve does not appear until the catheter tip is well below the level of the valve.

Despite this thesis, at times the diagnosis of infundibular stenosis comes as a surprise to the surgeon and the cardiologist at surgery. Fabricius,[21] in reporting on 50 patients submitted to pulmonary valvulotomy for either isolated pul-

monary stenosis or tetralogy of Fallot, had five cases in which catheterization was interpreted as revealing a valvular type of stenosis, and at operation infundibular stenosis was present. Antonius,[22] in reporting on 39 cases akin to those of Fabricius, found 11 cases of infundibular stenosis at surgery and only two were diagnosed by catheterization. This discrepancy has been commented upon by almost all groups with extensive experience in performing pulmonary valvulotomies.

Kirklin[13] has stated that a sudden transition from pulmonary arterial to ventricular pressure curve can occur not only in valvular stenosis but also in pure infundibular stenosis if the obstruction is situated close to the valve. Certainly this has been our own experience.

Only one of our three cases showed the classic pattern for an infundibular chamber. One other case (D.S.) which showed the pattern of a valvular stenosis may be explained by the fact that the infundibular constriction was situated just below the pulmonary valve. Despite multiple attempts to ease the catheter back through the valve and get an infundibular tracing in both Cases 1 and 2 (J. W. and D.S.), this could not be done.

It is of interest to examine the tracing of Case 1 (J.W.). Her pressure curve shows a classic Venturi effect. This pattern is characterized by the appearance of systolic negativity in the pulmonary arterial pressure tracings when the catheter is close to the valve. This is due supposedly to high velocity of blood flow through a narrowed orifice manifesting itself as a local fall in lateral pressure. The Venturi effect has been a common finding in patients with valvular stenosis, but we are unaware of its occurrence in a pure infundibular stenosis. It is difficult to explain this process in this patient because her infundibular canal was quite long and one would expect the jet effect of the stream to have been dissipated by the time the long canal had been traversed.

In each of our cases the right ventricular pressure curve did not appear until the catheter was well below the usual site of the pulmonary valve. We found this to be a valid observation and it was of great aid in confirming the diagnosis of infundibular stenosis.

Other methods of diagnosis: Rudhe[23,7] and the group at the Karolinska Institute in Sweden have used selective angiocardiography and electrokymography with excellent results in differentiating valvular from infundibular stenosis. We have had no experience with these techniques.

Differential diagnosis: The most difficult disease to differentiate from mild infundibular stenosis is the maladie de Roger. In mild infundibular stenosis the split of the second sound is wide and the thrill and murmur may be situated higher than in maladie de Roger. As the severity of the lesion increases, this differential diagnosis becomes much easier.[2]

Other entities that may simulate mild infundibular stenosis are atrial septal defect and mild aortic or subaortic stenosis. Severe infundibular stenosis with patent foramen ovale may mimic the tetralogy of Fallot.

Actually, for all practical purposes, the only differential diagnosis that is clinically important is that between severe infundibular stenosis with patent fora-

men ovale and tetralogy of Fallot. The types of procedure necessary to correct these lesions are quite different, so that an accurate preoperative diagnosis must be made. This usually can be accomplished clinically. Giant "a" waves in the neck, a right ventricular gallop, a long systolic murmur and thrill, a faintly audible late pulmonary component of the second sound, a moderately enlarged transverse diameter of the heart on x-ray, and marked right ventricular hypertrophy on the ECG favor a diagnosis of infundibular stenosis with patent foramen ovale. A history of squatting, normal jugular venous pressure and pulse, a short systolic thrill and a murmur, a loud single second sound, a right-sided aortic arch, normal to minimally enlarged transverse diameter of the heart on x-ray, and a moderate amount of right ventricular hypertrophy on the ECG favor the diagnosis of tetralogy of Fallot.

If this differential diagnosis cannot be made with certainty clinically, cardiac catheterization and dye dilution curves are helpful. On catheterization of an infundibular stenosis with patent foramen ovale, the catheter frequently can be passed through the patent foramen ovale and into the left side of the heart. In addition, the right atrial pressure is usually higher than one would expect in a tetralogy. The right ventricular systolic pressure is usually higher than the systemic systolic pressure. Injection of dye into the superior vena cava and again into the right ventricle will result, in the former case, in a bihumped type of curve due to the rapid appearance time of the dye because of shunting through the patent foramen ovale followed by the larger bolus of dye at the usual appearance time. In the latter case a fairly normal type of curve is observed. Catheterization of tetralogy of Fallot usually reveals a fairly normal right auricular tracing and pressure; the systolic pressure in the right ventricle will usually be equal to the systemic systolic pressure, and the catheter may be passed into the systemic circulation through the ventricular septal defect.

Dye dilution curves obtained with injection of the dye into the superior vena cava and the right ventricle will be almost identical. There will be a bihumped curve due to early appearance of the dye because of shunting across the ventricular septal defect into the aorta followed by the later appearance time of the dye which has followed the normal course through the heart and lungs.

Surgical Results.—Our patients were all operated on under hypothermia, as described previously.[24] If an infundibular stenosis is present, a chamber is frequently found beneath the level of the valve. The location of the systolic thrill at surgery is maximal over the infundibular stenotic site. Also, the infundibular chamber beats out of phase with the rest of the right ventricle. Therefore, if the preoperative diagnosis is valvular stenosis, simple observation and palpation at surgery will correct this impression, and instead of clamping off the main pulmonary artery and entering from above to relieve the stenosis, the operator will open the right ventricle, cut the fibrous band, and remove enough of the obstructing muscle mass to allow an adequate flow of blood into the pulmonary artery.

Symptomatically, all patients are much improved. They feel better and their exercise tolerance is increased. On physical examination, the thrill has

disappeared in all patients and the murmur has decreased in intensity. The second sound at the pulmonary area is now readily audible and split.

Postoperative catheterization revealed that in two cases (Cases 1 and 3) the pressure gradient was completely abolished. In the remaining case the pressure gradient was reduced, being 71 mm. Hg preoperatively and 36 mm. Hg postoperatively.

One of the cases (Case 3, L.H.), interestingly enough, now has pulmonary hypertension by catheterization, a diastolic shock in the pulmonary area on palpation, and a loud pulmonic component to the second sound. We have noted this phenomenon in patients following valvulotomy for valvular pulmonic stenosis.[25] This patient had an elevated pulmonary arterial pressure prior to surgery, and when the obstructing lesion was removed, there was a further rise in the pressure level. The thought that this patient has had multiple small pulmonary emboli or thrombosis of pulmonary arterioles has been considered. It will be of great interest to follow this patient's clinical course in the years to come.

The electrocardiograms of two patients has shown a significant diminution in the degree of right ventricular hypertrophy, while being unchanged in the third patient. It is of interest that the patient who had a drop in right ventricular pressure of 90 mm. Hg following surgery has shown no change in his electrocardiogram one and one-half years after the operation. X-ray examination postoperatively consistently shows an increase in heart size, particularly in the area of the right ventricle.

SUMMARY

We have reported three patients with isolated infundibular stenosis who have undergone surgical correction of the lesion. In two patients the pressure gradient has been completely abolished, and in the third the pressure gradient has been halved. All patients are symptomatically improved.

Infundibular stenosis comprises 3 per cent of all cases of pulmonary stenosis with intact ventricular septum.

Auscultation offers the most reliable aid in differentiating infundibular from pulmonary valvular stenosis. In infundibular stenosis the murmur and thrill are of maximum intensity in the second to third left intercostal spaces parasternally, or lower, and the murmur is always louder in the third left intercostal space than in the first left intercostal space. The quality of the murmur is considered to be more rasping in the infundibular variety.

Cardiac catheterization is diagnostic if an infundibular-chamber pressure curve can be demonstrated. In its absence, the finding of a transition zone between the pulmonary arterial pressure curve and the right ventricular pressure curve at a point much below the usual site of the valve should make one suspect infundibular stenosis.

It is important to differentiate preoperatively an isolated infundibular stenosis with a patent foramen ovale from the tetralogy of Fallot, because the surgical procedures and the risks involved are quite different. An infundibular stenosis can be successfully corrected by surgery with but a slightly higher risk than that in valvular stenosis.

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Clinical and Physiologic Studies in Ebstein's Malformation

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Ebstein's anomaly of the tricuspid valve was originally described in 1866.[1] A review of the problem in 1937, led Yates[2] to conclude that it was impossible to make the diagnosis during life. Engle,[3] in 1950, suggested that a clinical diagnosis was possible, and in the next year Soloff[4] reported the first case diagnosed during life. The total number of cases reported up to that time was 31, but since that year this number has grown steadily up to the present, the total now being about 90.[5-8] Through the experience gained by utilizing modern diagnostic techniques a clinical diagnosis can now be made with assurance, and this anomaly can be differentiated quite satisfactorily from certain other forms of cyanotic heart disease.

The basic morphologic defect in this condition is a downward displacement of one or more leaflets of the tricuspid valve so that the upper portion of the right ventricular cavity is incorporated into the right atrium and functions as part of the atrial cavity. The distal right ventricular cavity then becomes filled by a membranous sail-like sheet as a result of fusion of one or more of the tricuspid leaflets, leaving only a small chamber at the apex and the infundibular portion. The following case is presented to illustrate the typical clinical and physiologic abnormalities which this lesion produces.

The patient was a 34-year-old woman whose physical capabilities as a child were limited because of exertional breathlessness. An awareness of nail-bed cyanosis became apparent first at the age of 12, but not until the age of 15 was she told that a heart murmur was present. She grew to adulthood without any untoward events occurring. In spite of the perpetual complaint of fatigability, she worked as a telephone operator, married, and successfully bore one child at the age of 26. Finally, because of a gross hemoptysis in June, 1953, she came under medical surveillance again. From this time on she showed progressive deterioration, with repeated small hemoptyses, almost daily occurrences of sudden rapid heart action, and signs of cardiac failure. Sudden death occurred during sleep in June, 1954, at which time she was 35.

Clinical History.—Eighty-four per cent of the patients reported in the literature have been cyanotic, and a substantial delay in the appearance of this cyanosis was encountered in 37 per cent. The delay varied from 6 to 26 years.[7] The

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symptomatology was generally mild and some patients remained without complaints, particularly those who survived to an advanced age. The feature of relatively good exercise tolerance in the presence of considerable cardiomegaly may be of diagnostic aid. Cardiac arrhythmias are considered a frequent part of the clinical syndrome and about one third of the reported cases have shown paroxysmal atrial tachycardias, atrial flutter, or fibrillation. Because so many patients die suddenly, it is most likely that a disturbance in rhythm is implicated as the final event. Some die in congestive heart failure. Cerebral deaths as a result of paradoxical embolism through the coexisting defect in the atrial septum have claimed a few. Too frequently in recent years death has occurred during surgery, as the result of an erroneous diagnosis of Fallot's tetralogy. Evidently, the disease may also be benign and compatible with considerable longevity, since Adams[9] reported a case in a 79-year-old woman.

On examination this patient demonstrated moderate cyanosis, with both digital clubbing and conjunctival suffusion. The most striking finding was the unusual, even bizarre, nature of the auscultatory sounds over the precordium. A triple rhythm was present as a result of the presence of a loud third heart sound. A soft systolic murmur was heard maximally in the region of the apex, and a diastolic murmur was heard parasternally in the second and third left intercostal spaces. The first heart sound was of about normal intensity and best heard at the apex. The second sound was diminished over the base and best audible at the lower left sternal border. No evidence of cardiac failure was present.

Auscultation.—These same auditory features have come to be associated so commonly with this anomaly that McKusick[10] has stated that their presence in a patient with cyanotic heart disease should suggest immediately this particular malformation. This is especially true for the gallop rhythm, which occasionally may be double, resulting in a quadruple rhythm. In this situation the fourth heart sound resulting from contraction of the hypertrophied right atrium becomes prominent also. Occasionally, mid-systolic clicks occur, or sounds with the auscultatory characteristics of a friction rub further contribute to the unusual stethoscopic features of this problem. They are thought to coincide with the opening of the tricuspid valve.[11] Only 8 patients reported previously in the literature have demonstrated no murmurs at all.[7] The presence of the loud third heart sound appears to be the finding of sufficient distinction and incidence to be of real value in the diagnosis when fitted in with the other clinical findings.

Electrocardiography.—The striking electrocardiographic features in this patient are illustrated in Fig. 1. They are quite characteristic for Ebstein's anomaly. The majority of cases show an atypical right bundle branch block. The QRS interval measures 0.18 second in Lead V_2 in this case. The tracing shows an extremely low voltage of the initial deflections and excessive splintering, which are common observations. The broad R′ deflections of low amplitude seen in Leads II and III directly following a normally shaped R wave probably represent the delayed activation of the supravalvular or atrialized portion of the right ventricle. It has been suggested that these waves be referred to as P′ waves because of their similarity to P waves.[7] The first degree heart block, the impressive peakedness, increased amplitude, and increased duration of the P waves are

commonly observed abnormalities. The next most commonly observed defect is a Wolff-Parkinson-White syndrome, which occurs in slightly less than 10 per cent of the cases.[7] Sodi-Pallares[12] has concluded that this abnormality is so rare in other types of congenital heart disease that its presence should suggest Ebstein's malformation.

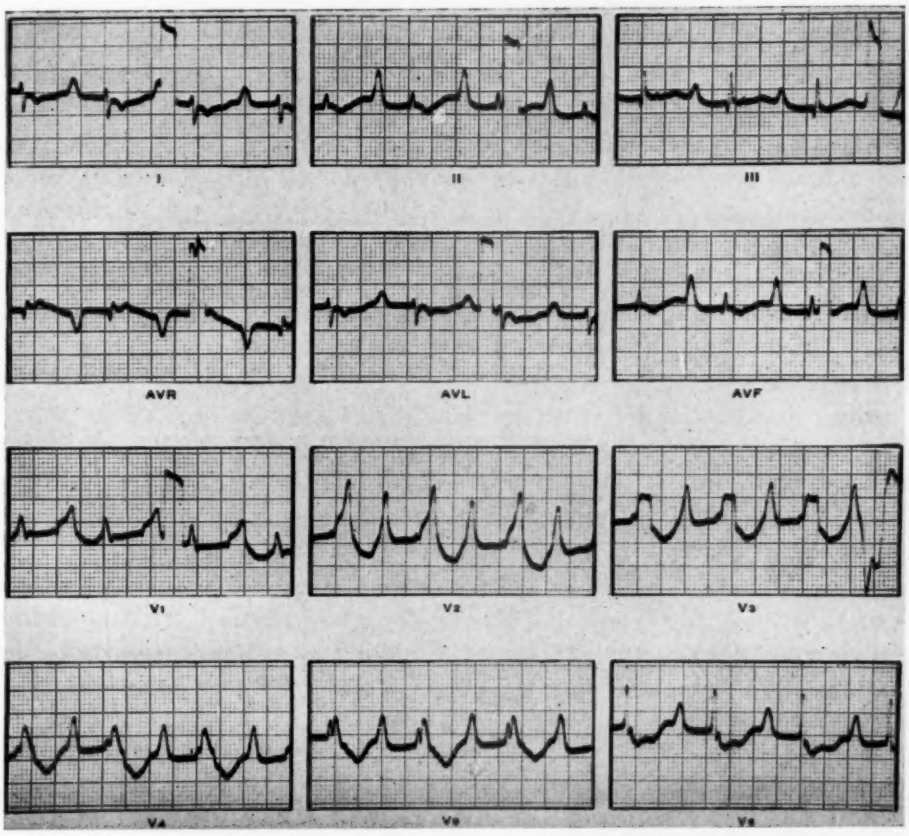

Fig. 1.—Typical electrocardiographic features of Ebstein's malformation are illustrated. Note the atypical right bundle branch block with the low amplitude R′ wave in Lead III which resembles a P wave. There are also giant P waves and first degree A-V block.

Roentgenography.—In the frontal projection (Fig. 2) the cardiac silhouette assumes a globular appearance and may be moderately to markedly enlarged, while the vascular pedicle appears relatively small. Fluoroscopically, pulsations are quite diminished in all dimensions, except for the middle portion of the left cardiac border in the area of the pulmonary conus where they are seen to be more vigorous. The scoliosis present in this patient alters the possibility of forming an impression about the degree of pulmonary vascularity, which ordinarily is strikingly decreased in Ebstein's disease. Furthermore, this patient developed a density in the right upper lung field, associated with increased markings following her first large hemoptysis; this density gradually cleared over subsequent weeks, and presumably was due to the presence of intra-alveolar blood. The increased

markings as seen here persisted, however. In the right anterior oblique projection (Fig. 3) the extreme density of the right atrial area is contrasted with the structures above it. Furthermore, the relatively clear lung fields are more notable in this view.

An angiocardiogram was recorded in this patient (Fig. 4), but the most desirable position for filming the heart was sacrificed in order to demonstrate simultaneously the right upper lung field, in which a possible pulmonary arteriovenous fistula was suspected. Nonetheless, the main diagnostic points can be appreciated. A huge right atrial chamber can be seen, and stasis of the opaque medium in this chamber for as long as 10 seconds after injection is characteristic. As a consequence of the diminished pulmonary blood flow, outlining of the pulmonary arterial system is quite poor and not really in evidence at 10 seconds. In addition, close study of the films revealed suggestive evidence of early opacification of the left atrium in the 3-second frame, as well as of the aorta in the 3.5-second frame, which indicates the presence of an interatrial shunt. The tremendous dilution resulting from right atrial stasis makes visualization of these latter chambers difficult, but this, too, is a diagnostic feature.

Soloff[4] and others have demonstrated a narrow, nonopacified band in the most anterior portion of the heart in the right anterior oblique projections; this band becomes clearly demarcated in the latter exposures. This is thought to be the displaced tricuspid leaflet which separates the small, functioning, distal right ventricle from its proximal "atrialized" portion; consequently, it is claimed to be of diagnostic significance.

Cardiac Catheterization.—This procedure is said to carry a greater than usual risk in these patients, but fortunately it was carried out successfully in this individual. Although only 41 of the 90 reported cases have been catheterized, the findings are so characteristic that the procedure is usually desirable in any diagnostic problem under consideration.[7,8]

The determinations of blood gas as revealed in Table I show evidence of an intracardiac right-to-left shunt by virtue of (1) resting arterial oxygen unsaturation, (2) an abnormal decrease in arterial oxygen saturation after exercise, and (3) an abnormally prolonged time to gain maximal saturation and failure to attain normal saturation even after 5 minutes of administration of oxygen. The latter observations, which are lower than the resting values, were made 30 minutes following exercise, and the initial saturation was still under the resting level when the administration of oxygen was begun. Vigorous voluntary hyperventilation not only failed to produce an increase in oxygen saturation but actually caused a striking decrease, indicating an inability to increase the pulmonary blood flow. This behavior is similar to that observed in both the tetralogy of Fallot and Eisenmenger's complex, in which a relatively fixed pulmonary resistance exists. This latter finding is contrary to the only previously reported similar studies. Van Lingen[13] reported two cases of Ebstein's anomaly in which a well-marked increase in arterial oxygen saturation occurred during hyperventilation and a fall during exercise in each case. Because this combination of events had not been found in any other type of cyanotic congenital defect, it was described as a distinctive diagnostic finding. The failure to show this par-

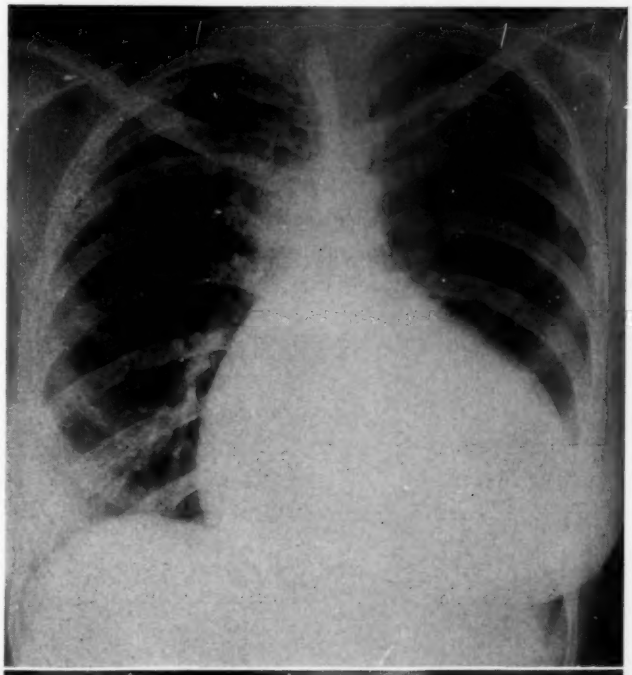

Fig. 2.

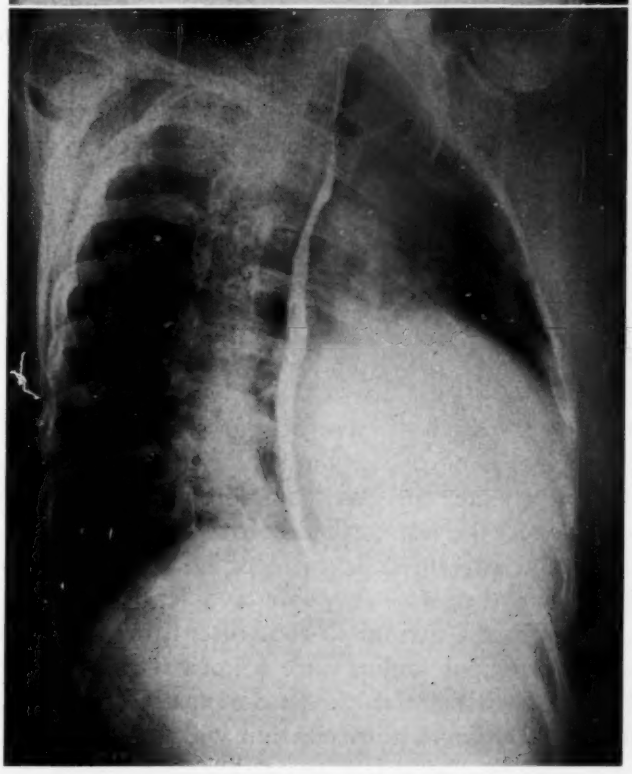

Fig. 3.

Fig. 2.—Teleoroentgenogram in frontal projection. The heart shows a globular type of configuration with a small vascular pedicle. Dorsal scoliosis distorts the pulmonary vascular markings in this case, but resolving linear strands are present in the right upper lobe, probably resulting from previous hemoptysis and intra-alveolar blood.

Fig. 3.—Right anterior oblique projection of the chest demonstrates the marked density of the right atrial area and decreased pulmonary vascularity.

ticular response to hyperventilation in this case may indicate an additional structural defect, possibly the type of pulmonary vascular disease discussed by Edwards[14] which occurs with the more severe cardiac lesions, causing reduced pulmonary blood flow.

To be noted also in Table I is evidence of a coexisting left-to-right shunt at the atrial level, clarifying definitely the site of the intracardiac communication. Arteriovenous shunting has been present in only 11 of the 41 reported cases in which catheterization has been carried out.[8]

TABLE I. OXIMETRY FINDINGS IN A 34-YEAR-OLD WOMAN WITH EBSTEIN'S DISEASE

ARTERIAL OXYGEN SATURATION (PER CENT)					
RESTING	VOL. HYPERVENTILATION	EXERCISE		O_2 ADMINISTRATION	
	AFTER 1 MIN.	1 MIN.	5 MIN. POSTEXERCISE	2 MIN.	5 MIN.
87	75	74	76	75	85

CARDIAC CATHETERIZATION—O_2 CONTENT (VOLUMES PER CENT)				
SVC	IVC	RA	RV	PA
7.9	—	13.9	13.2	12.2

The presence of a resting arterial unsaturation of 87 per cent and an oxygen gradient from the superior vena cava (SVC) to the right atrium (RA) indicates a bidirectional atrial shunt. Of particular interest is the further decrease in the arterial saturation to 75 per cent after vigorous hyperventilation, suggesting inability to increase pulmonary blood flow as a result of a fixed degree of pulmonary vascular resistance similar to that seen in severe pulmonary stenosis or Eisenmenger's complex and not previously reported in Ebstein's disease. Oxygen was administered in the postexercise period (see text).

Intracardiac pressure tracings have been of invaluable aid diagnostically in these cases. The typical abnormalities are shown in Fig. 5. As evidence of the greatly enlarged right atrium, the atrial pressure curve was recorded across the entire precordium over to the left cardiac border, and only along the uppermost portion were ventricular pressure curves recorded. This signifies displacement of the tricuspid valve to the left. A major technical difficulty in these cases is coiling of the catheter in the atrium so that oftentimes the ventricle cannot be entered. The other principal findings are a normal right ventricular and pulmonary arterial pressure, which are almost diagnostic in a cyanotic patient. In the acyanotic patient, cardiac catheterization will not be conclusive unless this condition is considered in the preliminary differential diagnosis.

Other pressure phenomena present in these tracings are of less diagnostic value but do contribute to an understanding of the altered hemodynamics present. Prominent systolic venous "a" waves can be seen in the atrial curves as a result of contraction of the large right atrium, and these waves can be seen to influence

the pressure patterns at all levels. This "a" wave probably can be considered to result from an impedance to normal emptying of the right atrium due to the very small volume of the distal portion of the right ventricle. Minor degrees of tricuspid stenosis have been demonstrated in some cases by a pressure gradient from the atrium to the ventricle as measured in diastole. Likewise, evidence of tricuspid insufficiency has been demonstrated occasionally, but in this case the pressure curves indicate a competent tricuspid valve.

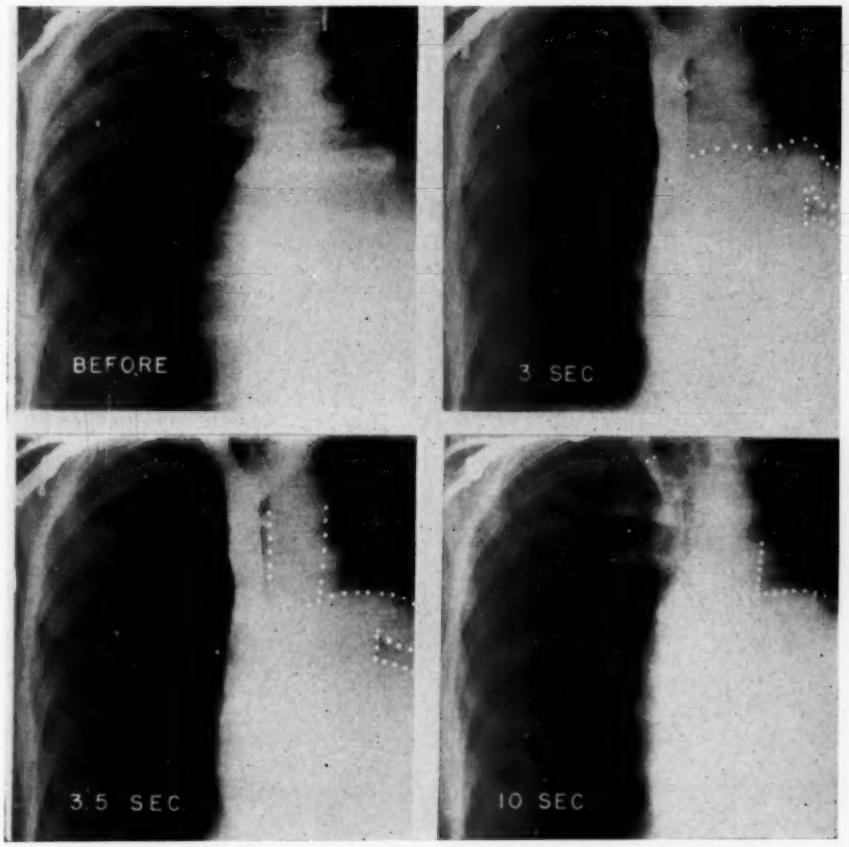

Fig. 4.—Angiocardiographic frames taken at 3, 3.5, and 10 seconds reveal stasis of the opaque media in the right atrium and inadequate filling of the pulmonary vascular tree even after 10 seconds. There is the suggestion of early left atrial and aortic opacification in the 3-second and 3.5-second frame, respectively. Right atrial dilution impaires a clear-cut visualization.

It may well be that the presence of the atrial contraction wave in ventricular diastole is a valuable aid in effecting maximum filling of the small distal portion of the right ventricle and thereby assures maximum output from this chamber.

Although not clearly demonstrated here, a systolic pressure gradient is frequently present between the right ventricle and the pulmonary artery. Since no actual pulmonic valvular stenosis can be found in the usual postmortem studies, this evidence of obstruction is probably a manifestation of a hypoplastic valve

ring and artery. Blount[5] reported a case in which pulmonary hypertension developed during exercise, suggesting further that the pulmonary arterial system is decreased in capacity.

A gradual rise and fall in the systolic right ventricular pressure curve is noted in the distal part of this chamber, and it is quite similar in form to the pulmonary arterial tracing. Next, there is demonstrated an unusual series of waves that vary considerably in configuration in different regions of the pulmonary artery. Sometimes the atrial contraction wave can be seen superimposed on the pulmonary arterial diastolic pressure curve. In fact, the right atrial pressure may sometimes equal or even exceed the pulmonary arterial pressure, so that it is not unlikely that atrial contraction may effect pulmonary arterial filling and contribute to pulmonary blood propulsion. In this way, the right atrium assumes the role of an accessory right ventricle.

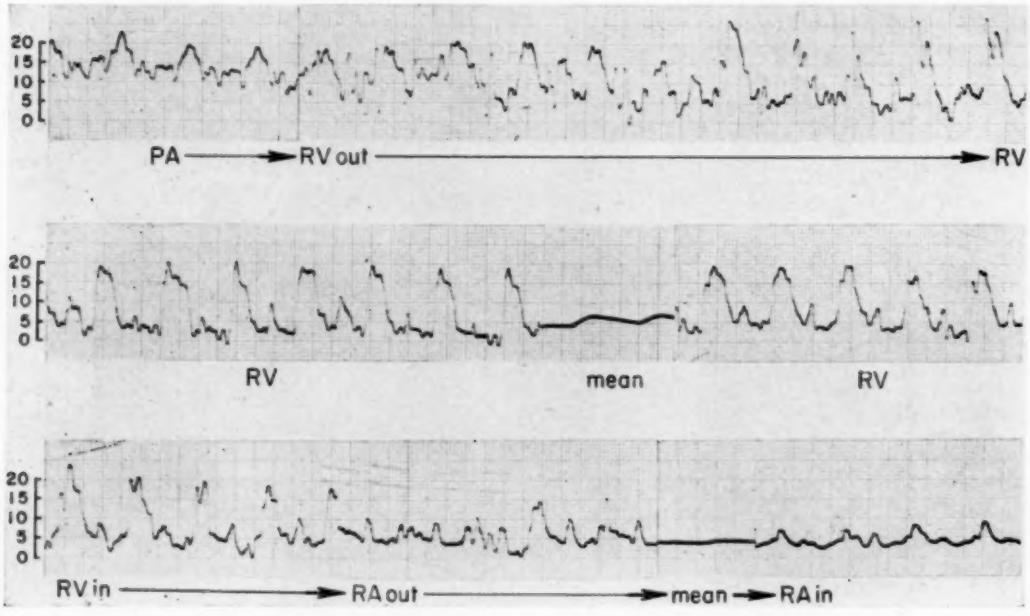

Fig. 5.—The intracardiac pressure tracings are of diagnostic significance because of the normal right ventricular and pulmonary arterial levels. Right atrial pressures were recorded over to the left cardiac border. In spite of the presence of artifacts, large "a" waves can be noted in the atrial pressure curve and also during diastole in the ventricular curve.

Another valuable diagnostic technique which is growing in popularity is the simultaneous recording of intracavitary electrocardiograms and pressure curves at the time of cardiac catheterization. The presence of low-pressure atrial-type curves recorded simultaneously with an endocardial exploring electrode showing complexes of ventricular configuration is of definitive diagnostic significance.[15]

Physiologic Defects.—In reviewing the physiologic defects present in the light of the clinical diagnostic findings in this patient it can be said that ineffectual right atrial emptying, limited by the small right ventricular capacity, in addition

to incoordinated atrial and proximal right ventricular systole, leads to a marked reduction in pulmonary blood flow. As a result, right atrial dilatation and increased right atrial blood volume ultimately lead to an increase in pressure and a right-to-left shunt with accompanying cyanosis in the presence of an atrial septal defect or patent foramen ovale.

Fig. 6.

Fig. 7.

Fig. 6.—Anatomic demonstration of the defect. The large lower chamber is the cavity of the atrialized right ventricle, the floor of which consists of a deformed sheet-like tricuspid valve with several fenestrated openings. Above this to the right is the right atrial cavity. To the left can be seen a small patent foramen ovale.

Fig. 7.—The patent foramen ovale measured 6 mm. in diameter and permitted bidirectional shunting of atrial blood.

Necropsy.—The postmortem examination of the heart in this patient revealed a classic Ebstein's malformation associated with a patent foramen ovale. The entire anterior surface of the heart was occupied by the right atrium and auricular appendage. The main abnormality was in the tricuspid valve, the leaflets of which were not only abnormal in origin but also in structure, forming a large curtain which arose from the wall of the right ventricle and the septum below the valve ring. Communication with the right ventricle was permitted through several small fenestrations in this membranous sheet, and there was complete absence of true valve cusps. Only a part of the leaflet representing the anterior cusp arose from the annulus fibrosus. The papillary muscles and chordae were either very poorly formed or absent (Figs. 6 and 7).

The abnormal valve divided the right ventricle into two chambers. The proximal portion was thin-walled, dilated, and appeared as part of the atrium. The right atrium itself was hugely dilated and hypertrophied. The distal portion of the right ventricle was limited mainly to the outflow chamber, and the volume of the cavity was quite small.

A patent foramen ovale measuring 6 mm. in diameter was present and obviously served as the site of shunting.

Associated cardiovascular abnormalities have not been commonly reported, but this patient demonstrated three that deserve mention. The pulmonary arteries were quite hypoplastic, and the circumference at the pulmonary ring measured only 2.6 cm. Also, the valve was quite abnormal in that it consisted of a single thin leaflet shaped somewhat like a funnel. Furthermore, the mitral valve was deformed also and presented a thick bar of tissue across the commissural opening so that two small openings existed, with relative rigidity of the leaflets. Essentially, in the opinion of the examining pathologist, a state of mitral stenosis was present.

Differential Diagnosis.—The conditions most likely to be confused with this anomaly are those characterized by reduced pulmonary blood flow, such as pulmonary stenosis with or without a septal defect, tricuspid atresia, and especially Fallot's tetralogy. The acyanotic form of the anomaly presents a more difficult problem and is confused with pulmonary stenosis with intact septa, in which case a clinical differentiation may be impossible. In the adult an acquired cardiac lesion presents the chief diagnostic problem.

SUMMARY

A case has been presented which exemplifies the typical clinical, laboratory, and anatomic features of Ebstein's disease. With modern diagnostic techniques the diagnosis can now be made with assurance during life. The main criteria for establishing a correct diagnosis are late or absent cyanosis, radiographic evidence of right atrial and right ventricular enlargement without signs of pulmonary vascular congestion, and pressures in the pulmonary artery and right ventricle which are within the normal range. From these studies a fairly distinctive differentiation emerges.

The author wishes to express appreciation to Dr. James E. Kreisle, of Austin, Tex., for his referral of this patient, and to Dr. Charles F. Pelphrey of Austin, Tex., who performed the necropsy examination and made available the anatomic photographs.

ADDENDUM

Since this paper was originally presented, additional cases have been reported by Kezdi and Wennemark[16] and by Vacca and his associates.[17]

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Intravenous Injection of Hyaluronidase in Acute Myocardial Infarction: Preliminary Report of Clinical and Experimental Observations

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Since the discovery of the spreading factor, hyaluronidase,[1,2] a study of its pharmacologic properties has come from biochemists, oncologists, endocrinologists, gynecologists, pharmacologists, and internists. The spreading factor has been identified as a mucolytic enzyme, whose main action is depolymerization and hydrolyzation of hyaluronic acid, a polysaccharide which is an essential component of intercellular ground substance.[3] In Duran-Reynals own words, "spreading was shown to be the result of the effect of this enzyme on a medium which, normally viscid and acting as a barrier, becomes a medium with a viscosity presumably close to that of water."[4]

Various investigators have exploited this action of hyaluronidase in enhancing the absorption of parenteral fluids and drugs, in the treatment of infertility, in infant urography, in preventing urinary calculi, in the treatment of pulmonary edema, etc.[5-8] In all of these instances the administration of hyaluronidase has been local, i.e., direct contact with the substrate.

Many would question the advisability of intravenous administration of hyaluronidase for clinical use because of the presence of certain hyaluronidase inhibiting factors in the serum. Seifter,[9] however, has demonstrated that intravenous hyaluronidase produces a spreading activity in the plasma lasting up to 5 hours, with the peak of action 5 minutes after administration. He also demonstrated the presence of the spreading factor in the urine after intravenous administration of the enzyme, which indicates that a fraction of the administered dose of hyaluronidase traverses capillary walls and is apparently not fully altered, if at all, within the circulatory system.

The first report regarding the clinical use of intravenous hyaluronidase was made in 1954, by Sa Earp,[10] who applied this enzyme in patients with cerebral edema. He observed fast recovery in the level of consciousness and improvement of the neurological signs in all cases.

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In 1955, one of us administered this enzyme intravenously in cases of acute myocardial infarction.[11] Knowing that intramyocardial edema (the existence of which has been proved by Buchner[12] with experimentally produced acute coronary insufficiency in rabbits) probably plays an important role in the initial stages of this condition,[13] we wanted to find out what hyaluronidase might do in altering this pathology. The results at that time, whether related or not to hyaluronidase, were very gratifying, and have motivated us to pursue this experiment in the past few months in order to better assess the use of intravenous hyaluronidase in acute myocardial infarction.

MATERIAL AND METHODS

At the present time a series of studies on dogs is well under way in our research laboratories to evaluate the actual meaning and efficiency of this enzyme in experimentally produced acute coronary insufficiency. To date, we have also applied intravenous hyaluronidase to 6 patients with acute myocardial infarction. The reason we have used it on so few is that very rigorous criteria are applied for the selection of patients to whom hyaluronidase should be administered. First of all, the patient must be seen within 8 hours after the onset of the pain. Secondly, definite electrocardiographic changes of acute and severe injury to the cardiac muscle must exist, i.e., S-T elevation and T-wave changes in the leads directly facing the damaged area; Q waves may or may not be present. These criteria are applied so that we may be absolutely sure that we are not dealing with angina pectoris, in which case recovery might be spontaneous. In the 6 patients who fulfilled the above criteria, we used a special preparation of hyaluronidase, consisting of 100,000 units of Wydase.* We applied the following schedule for our treatment: 100,000 units of Wydase in 10 c.c. of 5 per cent glucose in water, intravenously, every 6 hours for the first 24 hours; then the same dosage every 8 hours for 2 more days; and finally, the same dosage every 12 hours for another 2 days. The treatment was then discontinued, since it was believed that all changes produced by the edema must have subsided in this period of time.

CASE REPORTS ON PATIENTS

CASE 1.—I. S., a 62-year-old white man, suddenly developed severe substernal pain radiating to both shoulders. On admission, the blood pressure was 90/60 mm. Hg, the pulse rate was 92, the heart sounds were normal, and the transaminase was 190 units. The first electrocardiogram was taken 4 hours after the onset of pain (Fig. 1), and the patient immediately received an intravenous injection of Wydase (100,000 units) in addition to our routine treatment (oxygen tent, morphine, anticoagulants, and bed rest). The second electrocardiogram was taken 2 hours after the first administration of Wydase (Fig. 1).

CASE 2.—W. R., a 57-year-old white man, was admitted for severe chest pain of 2 hours' duration. The blood pressure was 140/100 mm. Hg, the pulse rate was 64, the heart sounds were normal, and the transaminase was 90 units. The first electrocardiogram was taken 2½ hours after the onset of the pain (Fig. 2). Intravenous Wydase (100,000 units) was then started, and another electrocardiogram was taken 4 hours later (Fig. 2). In addition, this patient received the usual routine care.

CASE 3.—G. T., a 62-year-old white man, was admitted with severe chest pain of 3 hours' duration associated with profuse diaphoresis. The blood pressure was 108/80 mm. Hg, the pulse rate was 68, the heart sounds were distant, and the transaminase was 163 units. The first electrocardiogram was taken 3½ hours after the onset of the pain (Fig. 3), and intravenous Wydase (100,000 units), as well as our routine treatment, was given to the patient. A second tracing was taken 5 hours later (Fig. 3).

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*This special preparation of hyaluronidase was obtained from the Wyeth Laboratories for our investigational use.

CASE 4.—L. D., a 65-year-old white man, was admitted with severe, localized substernal pain of 1 hour's duration. The blood pressure was 140/80 mm. Hg, the pulse rate was 75, the second heart sound was accentuated over the pulmonic area, and a Grade 2 systolic murmur was heard over the whole precordium. The transaminase was 167 units. The first electrocardiogram was taken 1½ hours after the onset of the pain (Fig. 4). Routine treatment was initiated, and intravenous Wydase was given in the same dosage as that used in the preceding cases. Three hours later another tracing was recorded (Fig. 4).

CASE 5.—J. L., a 54-year-old white man, was admitted with severe chest pain of 3 hours' duration, radiating to the left arm. His history revealed several attacks of angina pectoris in

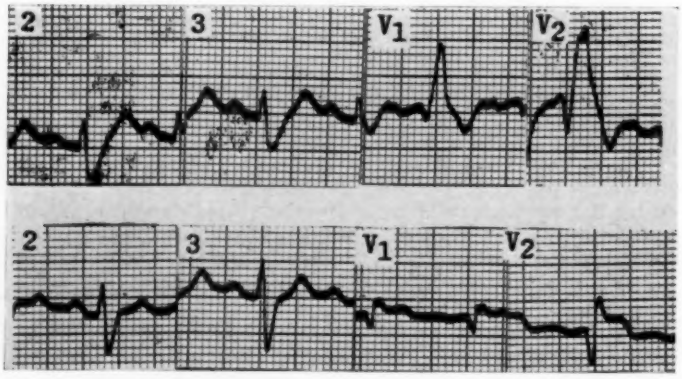

Fig. 1.—Extensive anterior infarction with disturbance in the right ventricular conduction. Notice the marked decrease in the duration of the QRS complex 2 hours after the intravenous administration of Wydase. *A*, Before. *B*, After.

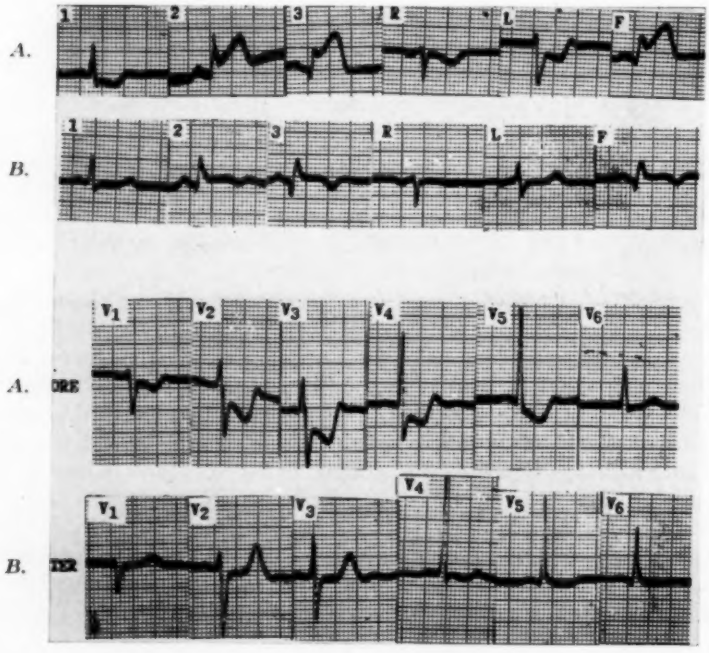

Fig. 2.—Acute diaphragmatic infarction. Observe the changes in the S-T segment 4 hours after the initial dose of Wydase. *A*, Before. *B*, After.

the past 10 years. The blood pressure was 150/85 mm. Hg, the pulse rate was 42, the first heart sound was periodically accentuated, and the second sound was normal. The transaminase was 92 units. The first electrocardiogram was taken 6 hours after the pain had started, and showed complete A-V block (Fig. 5). Intravenous Wydase (100,000 units), as well as oxygen, morphine, and anticoagulants were given to the patient. Eight hours later a second electrocardiogram revealed that the complete A-V block had disappeared, although S-T changes were very much accentuated (Fig. 5). Twenty-four hours later a third record showed significant improvement of the ventricular repolarization (Fig. 5).

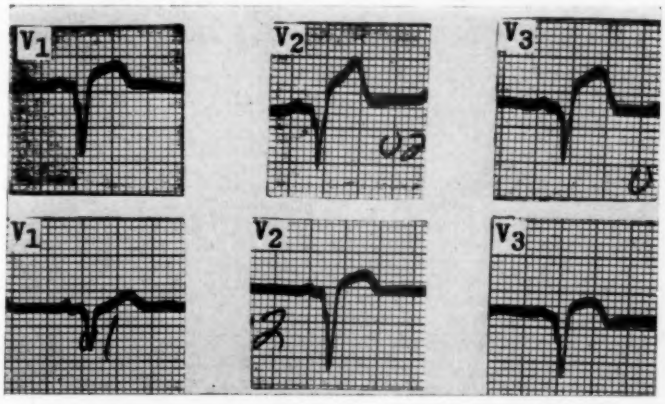

Fig. 3.—Acute anteroseptal infarction. Notice the changes in the S-T segment 5 hours after intravenous hyaluronidase had been started. *A*, Before. *B*, After.

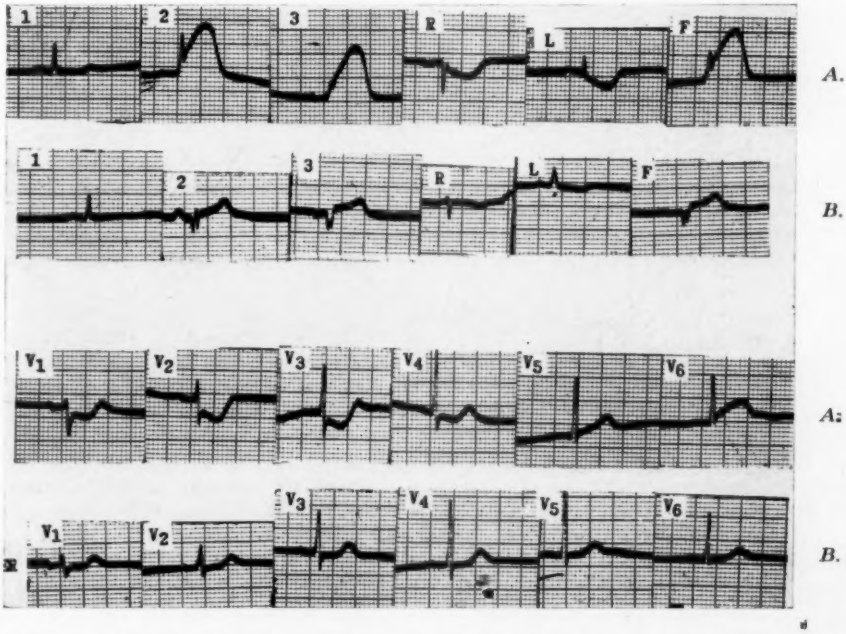

Fig. 4.—Acute diaphragmatic infarction extending to the dorsal regions. The "current of injury" in Leads II, III, and aV_F shows a typical "monophasic wave" in the first tracing. Notice the marked improvement in the S-T segment 3 hours after hyaluronidase had been injected intravenously. *A*, Before. *B*, After.

CASE 6.—L. H., a 46-year-old white woman, suddenly developed moderate chest pain, constrictive in character, and radiating to the neck. Within 1 hour she had spontaneous relief of the pain, but developed a severe headache. She has had several such attacks since the age of 35.

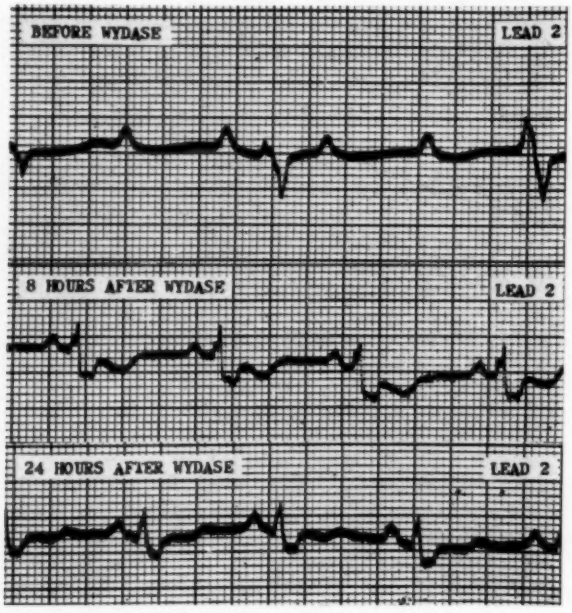

Fig. 5.—Acute anterolateral infarction (mirror image in Lead II); complete A-V block which converted to sinus rhythm 8 hours after Wydase. Observe how the depressed S-T segments seen in the second electrocardiogram shifted toward normal in the third one.

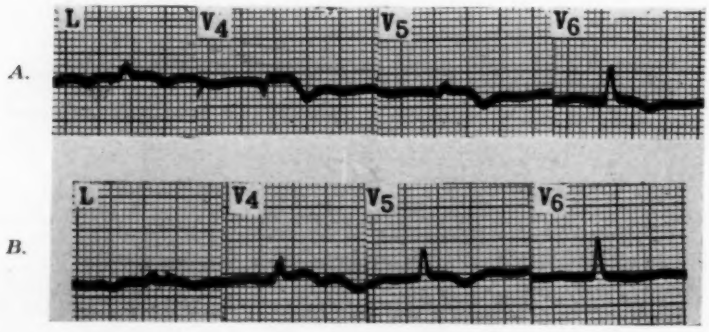

Fig. 6.—Acute anterolateral infarction. S-T elevation is less pronounced 7 hours after Wydase. *A*, Before. *B*, After.

On admission, the blood pressure was 110/65 mm. Hg, the pulse rate was 75, the heart sounds were normal, and the transaminase was 62 units. The first electrocardiogram was taken 3 hours after the onset of the chest pain (Fig. 6). Intravenous Wydase (100,000 units) was started, and the patient was placed in an oxygen tent. The second tracing was taken 7 hours later (Fig. 6).

Comment: All patients had an uncomplicated clinical course and were discharged in good condition within 4 to 6 weeks after admission.

REPORT OF STUDIES ON DOGS

Acute coronary occlusion was produced in a group of 7 dogs by ligation of branches of the coronary arteries. In 1 of the dogs the standard limb leads were used to record the electrocardiographic changes; in the other 6, direct epicardial leads were applied. The following results were obtained.

Dog No. 1.—Immediately after the ligation of the anterior descending branch of the left coronary artery, S-T elevation was observed in the ECG (Fig. 7). We then injected 100,000 units of Wydase intravenously, and in a few minutes the S-T segment shifted back to normal (Fig. 7). This dog was kept under observation, receiving the enzyme in the same dosage every 12 hours for 60 hours. Transaminase was up to 620 units 48 hours after the ligation, in spite of the fact that the electrocardiogram did not show any pattern of injury (S-T elevation). After the sixtieth hour, we sacrificed the dog, and the anatomicopathologic examination revealed a large area of myocardial infarction with moderate organization of collateral circulation spreading from the periphery.

Dog No. 2.—Two minutes after the ligation of the anterior descending branch of the left coronary artery, a severe "current of injury" developed (Fig. 8). Immediately, 100,000 units of Wydase was injected intravenously. Two minutes after the injection the amplitude of the S-T segment had decreased, and in 10 minutes only slight elevation of this segment was present (Fig. 8).

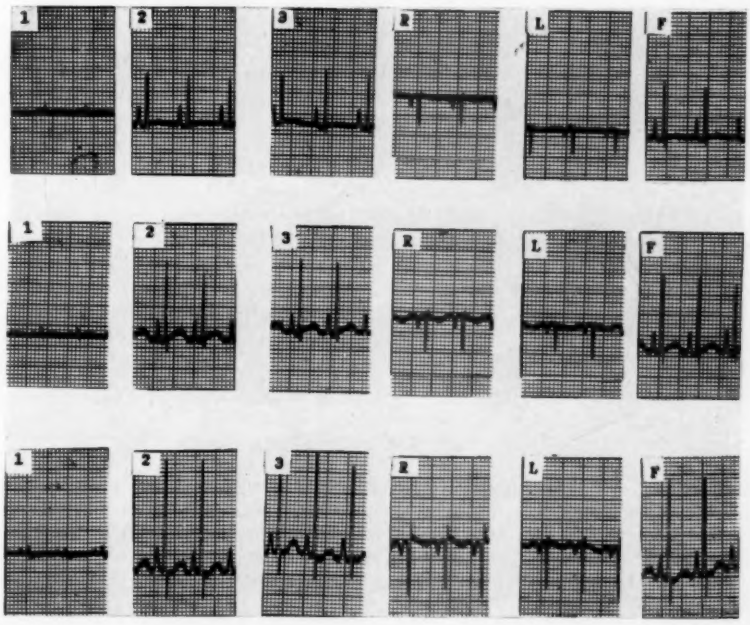

Fig. 7.—Peripheral leads of a dog in which a ligature was placed at the terminal portion of the anterior descending branch of the left coronary artery. Notice in Leads II, III, and aVF the S-T elevation 5 minutes after the ligation, and how this segment became isoelectric again 5 minutes after the intravenous administration of Wydase. *A*, Before ligation. *B*, Five minutes after ligation, before Wydase. *C*, Five minutes after Wydase, with the artery still ligated.

Dog No. 3.—After we had recorded a control epicardial electrocardiogram, the anterior descending branch of the left coronary artery was ligated. Two minutes later, marked S-T elevation was noted (Fig. 9). Ten cubic centimeters of saline was injected intravenously in order to observe what effect this might exert. A tracing taken 1 minute after this injection showed accentuated changes in the S-T segment (Fig. 9). Immediately, 100,000 units Wydase was in-

jected intravenously, and within 5 minutes we noted marked diminution of the "current of injury" (Fig. 9). One hour later, since no other changes appeared in the record, we removed the ligature, and the S-T segment became isoelectric almost immediately and ischemic T waves developed (Fig. 9). On the following day peripheral leads recorded in this dog revealed no abnormality.

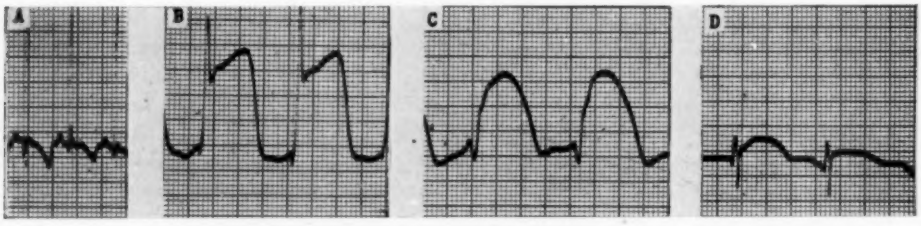

Fig. 8.—Epicardial lead at the apex of the left ventricle in dog. *A*, Before ligation. Isoelectric S-T segment. Paper speed 25 mm./sec. *B*, Two minutes after ligation of the anterior descending branch of the left coronary artery. Observe the appearance of a marked "current of injury." Paper speed 50 mm./sec. *C*, Changes in the S-T segment 2 minutes after the intravenous injection of Wydase. Paper speed 50 mm./sec. *D*, Ten minutes after Wydase. The S-T segment became almost isoelectric.

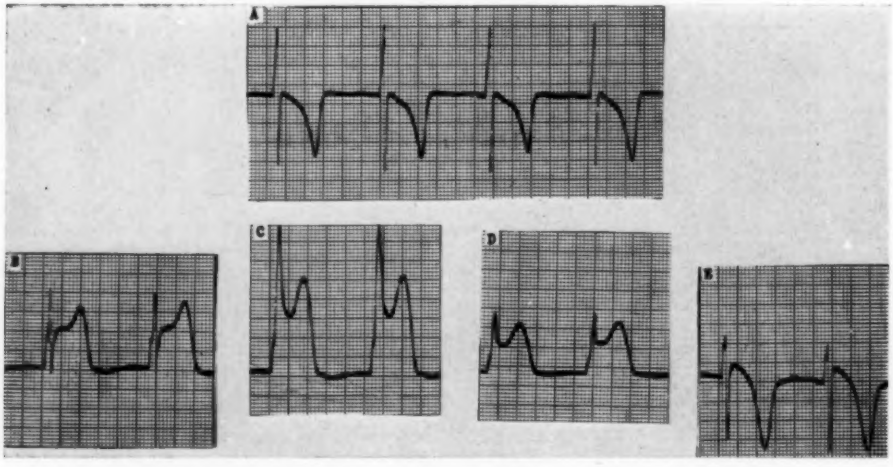

Fig. 9.—Epicardial lead close to the apex of the left ventricle in dog. Paper speed 50 mm./sec. *A*, Before ligation of the anterior descending branch of the left coronary artery. *B*, Two minutes after ligation. Marked S-T elevation. *C*, One minute following intravenous injection of 10 c.c. of saline. The S-T segment became more elevated. *D*, Five minutes after Wydase. Marked diminution of the "current of injury." *E*, Immediately after the ligature had been removed. S-T segment almost isoelectric; ischemic T waves.

Dog No. 4.—The anterior descending branch of the left coronary artery was ligated, and the changes in the S-T segment were observed for 1 hour after the ligation. S-T elevation appeared after 1 minute and was markedly accentuated after 10 minutes (Fig. 10). At the end of 1 hour, a pronounced "current of injury" was still present (Fig. 10). No hyaluronidase was injected in this dog, in order that we might compare the tracing with those taken on dogs in which hyaluronidase was used.

Dog No. 5.—After the ligation of the anterior descending branch of the left coronary artery, significant S-T elevation appeared (Fig. 11). Wydase was injected intravenously (100,000 units), and 10 minutes later the S-T segment was markedly improved (Fig. 11). Wydase was then injected intravenously with Evans blue dye in order to confirm the presence of the enzyme in the

affected area of the myocardium. In a few minutes all the collateral vessels surrounding the damaged region became colored by the dye. At that moment the electrocardiogram showed a severe "current of injury," which, in our opinion, was due to the Evans blue, since it disappeared immediately after another intravenous injection of Wydase (100,000 units) (Fig. 11).

Dog No. 6.—After the ligation of the ramus primus of the anterior descending branch of the left coronary artery, marked S-T elevation developed (Fig. 12), and then 100,000 units of Wydase was injected intravenously. In 5 minutes the S-T segment had improved (Fig. 12).

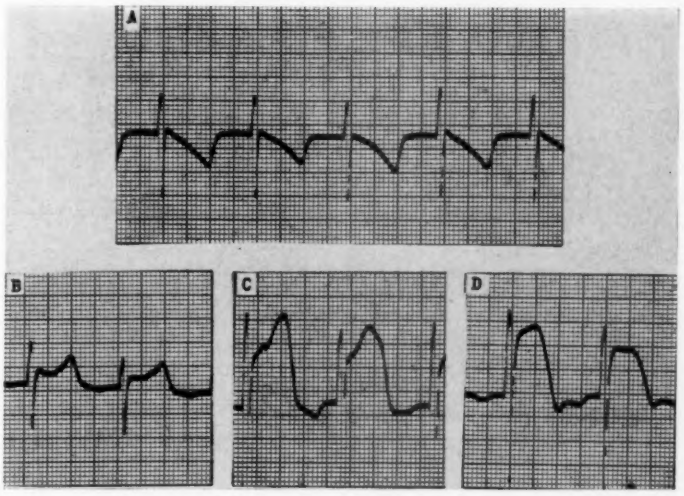

Fig. 10.—Epicardial lead close to the apex of the left ventricle in dog. Paper speed 50 mm./sec. Control study. *A*, Before ligation. *B*, *C*, and *D*, Electrocardiographic changes 1 minute, 10 minutes, and 1 hour, respectively, after ligation of the anterior descending branch. No spontaneous improvement in the S-T segment was observed. No Wydase was injected into this dog.

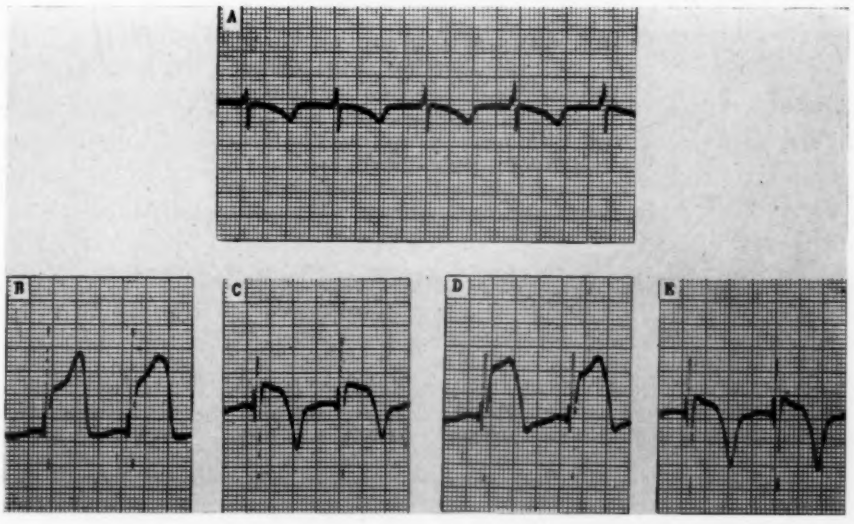

Fig. 11.—Epicardial lead close to the apex of the left ventricle in dog. Paper speed 50 mm./sec. *A*, Before ligation. *B*, Three minutes after ligation. Marked S-T elevation. *C*, Ten minutes after Wydase. S-T segment improved. *D*, Three minutes after intravenous injection of Wydase with Evans blue. S-T became again markedly elevated. *E*, Three minutes after another injection of Wydase. S-T segment is again improved.

Thirty minutes after ligation another injection of the enzyme (100,000 units) was given intravenously, and in 5 minutes the S-T segment became almost isoelectric (Fig. 12). This dog was sacrificed 2 hours later, and the anatomicopathologic examination did not reveal any evidence of myocardial damage.

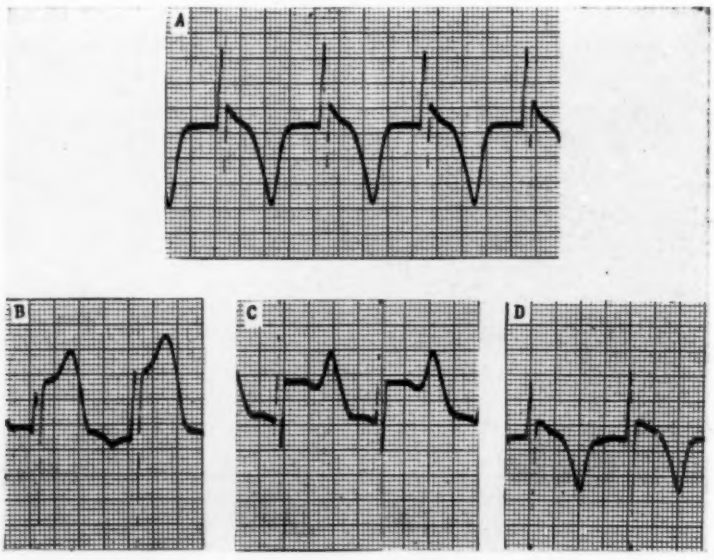

Fig. 12.—Epicardial lead close to the apex of the left ventricle in dog. Paper speed 50 mm./sec. *A*, Before ligation. *B*, Two minutes after ligation. Marked S-T elevation. *C*, Five minutes after Wydase. Improvement of the S-T segment. *D*, Thirty-five minutes after ligation and 5 minutes after a second injection of Wydase. S-T segment is now almost isoelectric.

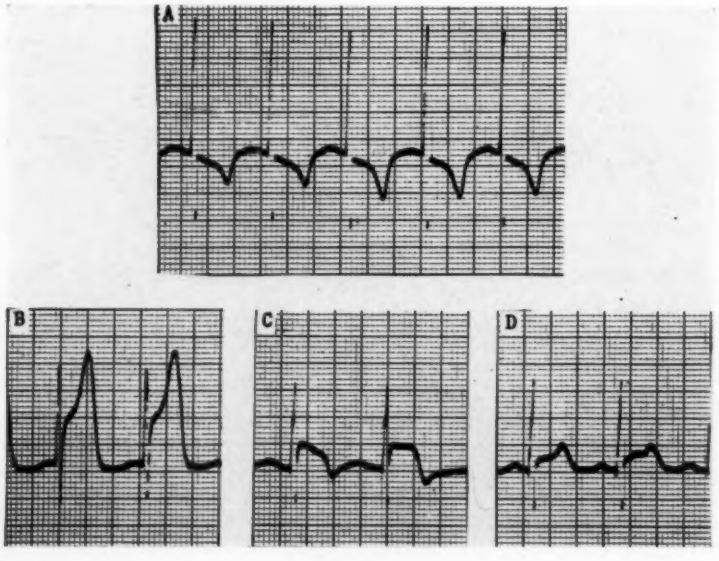

Fig. 13.—Epicardial lead close to the apex of the left ventricle in dog. Paper speed 50 mm./sec. *A*, Before ligation. *B*, Five minutes after ligation. Pronounced ST-T changes. *C*, Five minutes after Wydase (200,000 units). ST-T shows marked improvement. *D*, Ten minutes after Wydase. The "current of injury" practically disappeared. Positive T waves are probably due to the persistence of some degree of subendocardial ischemia.

Dog No. 7.—After the ligation of the ramus primus of the left coronary artery, pronounced ST-T changes appeared (Fig. 13), and an immediate injection of 200,000 units of Wydase intravenously was made. In 5 minutes the ST-T showed marked improvement, and in 10 minutes the "current of injury" practically disappeared, although the T waves became positive (Fig. 13). We think that these changes in the polarity of the vector of repolarization (T vector) can be explained by persistence of some degree of subendocardial ischemia.

PHYSIOPATHOLOGIC DISCUSSION

Whenever an arterial vessel is partially or totally obliterated, a state of tissular ischemia and anoxia develops beyond the site of the obstruction. This anoxia produces an increase in the permeability of the capillaries of the affected area, with consequent augmentation of the interstitial fluid.[14] Although these basic physiopathologic principles can be applied also to the coronary circulation, the presence of myocardial edema in acute coronary occlusion has been described only by Buchner,[12] in 1939. This edema not only impairs the metabolic changes of the cardiac fibers, but also impedes the beneficial action of a possibly existent collateral circulation by compressing the collateral vessels, thereby producing a diminished blood flow. The edema affects the cardiac cells by both mechanical and physiobiochemical actions. Mechanically, the excessive tissular fluid injures the myocardial fibers by compression. Physiochemically, it acts by disturbing the electrolyte changes (potassium and sodium) through the cellular membrane. As a result, an electrical gradient (difference of potential) appears between the damaged and normal areas of the myocardium; this gradient is electrocardiographically represented by a "current of injury"—S-T elevation.

Of course, the edema is only one of the multiple factors involved in the myocardial changes that follow an acute coronary occlusion. Others, such as the degree of anoxia and ischemia, the extension of the affected area, and the condition of the collateral circulation, are also extremely important and play a significant role in the evolution of the process.[15,16]

It is our opinion that if we can reduce the action of any of these factors which have a detrimental effect upon the cardiac muscle, we may well be shifting the evolution toward a better prognosis. On the basis of all of the concepts mentioned above, we believe that hyaluronidase reduces the edema in the damaged myocardial area, thus decreasing the injury to the cardiac fibers during the critical first hours that follow the acute coronary occlusion, and that it also facilitates the beneficial action of a possibly existent collateral circulation. In all of our patients the S-T segment shifted toward normal within 2 to 24 hours. In 5 patients these changes occurred before the seventh hour, which was exceptional and not to be expected under other conditions. Actually, we have never seen such changes occur so rapidly in patients in whom Wydase was not used. In the same way, it is not common to observe the rapid improvement in disturbances of conduction that happened in 2 of our patients.

We are not certain whether the mechanism of action of hyaluronidase depends upon a spreading of the edematous process or upon increased capillary reabsorption. It is possible that both conditions coparticipate, and it is also admissable that other factors, as yet unknown to us, may be involved.

Although the results of the present study are very promising, we realize that many more experiments and clinical observations must be carried out before hyaluronidase can be accepted as an efficient therapeutic weapon in the treatment of acute myocardial infarction.

UMMARY

A preliminary communication is presented on the intravenous injection of hyaluronidase in acute myocardial infarction.

Six cases are reported and electrocardiographic changes are shown after the administration of the drug. The results of studies in seven dogs are reported.

Apparently, hyaluronidase acts by reducing intramyocardial edema during the acute phase following coronary occlusion. The physiopathology of this intramyocardial edema is discussed, as well as the possible mechanisms of action of this enzyme.

The authors stress the necessity of further investigations before hyaluronidase can be accepted as an efficient drug in the management of acute myocardial infarction.

The authors are indebted to Helen Kleinhenz, R.N., Marjorie McIntyre, R.N., and Frank Minello, Hospital Photographer, for their collaboration in this study. We also wish to thank João Tranchesi, M.D., who gave valuable assistance in the preparation of this manuscript.

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Experimental and Laboratory Reports

Comparison of Three Different Systems of Vectorcardiography

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The development of vectorcardiography is still hampered by the great number of different lead systems. To arrive at a greater uniformity a comparison of these systems is necessary. This has been done by several investigators,[1-8] but the ever-increasing number of lead systems makes it worth while to proceed with this work.

This investigation must not be restricted to phantom measurements, for it is essential to compare systems by applying them to real human bodies. This is the more urgent since vectorcardiography can become an important means of cardiac diagnosis only when the differences between the current lead systems are less than the small differences existing between normal and pathologic borderline cases.[9]

The number of lead systems proposed up until now is, however, so great that a two-by-two comparison would be an endless task. Therefore, we have confined our research to three systems, viz., those developed by Frank[10] and Schmitt,[11] and one of our own. As to the latter we have chosen a system with five electrodes, three at the extremities, one precordial, and one at the back.[12]

METHOD

In all three systems two forms, a more accurate one and a simplified one, have been proposed. To propagate the application of vectorcardiography in practice we have chosen the simplest form of each.

1. In Frank's paper describing his lead system[10] the more accurate method involves a determination of the height of a transversal section of the trunk on which five electrodes are situated,

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by means of an extra measurement. We have refrained from this refinement in applying these electrodes at the height mentioned by Frank as being adequate in most cases, viz., at the fifth intercostal space near the sternum.

The head electrode is not applied in the position chosen by Frank, but to the forehead. This makes little difference and is easier to perform.

The combination of the leads necessary to obtain the three orthogonal components of the heart vector is realized with the aid of our previously described universal vectorcardiograph.[13] The relatively great number of electrodes compels us to use two extra resistances, between subject and instrument, so as to arrive at the correct linear combination of lead voltages. The photographs of frontal and horizontal projections have to be taken successively.

2. The simpler Schmitt system SVEC II is used. The head electrode is applied to the forehead, just as in the preceding case. Frontal and horizontal projections are taken simultaneously.

3. Our own system is composed of two systems, as published earlier, B_1[1] and W_4''.[6] The first, with an electrode on the sternum, emphasizes the effect of the anterior part of the heart muscle, while W_4'' emphasizes its posterior part. We give them equal weight, so that the orthogonal components of the heart vector are the arithmetic means of the linear functions of the lead voltages of both systems, B_1 and W_4''. As a simplification we use a single electrode on the sternum and refrain from a fivefold precordial electrode as mentioned previously.[12] The frontal and horizontal projections are taken simultaneously.

The application of the electrodes is made with not more care than can be expected in clinical use, omitting the extra accuracy which could be attained in laboratory work. The number of electrodes of these three lead systems (Frank, Schmitt, and B_1W_4'') is 7, 6, 5, respectively. Their diameter is 2.5 or 4 cm., depending on the space available. The three systems have been compared on 65 normal subjects and 124 cardiac patients. Since in the systems of Frank and Schmitt the scale has been left undetermined by the authors, we have measured corresponding dimensions of the loops in the three systems and have so chosen the sensitivity that in the mean the loops of the three systems are of the same size.

As formerly,[1,6] we indicate the agreement of the vectorcardiograms from two different lead systems with a score of 0 to 10. Later, this method of grading has been applied by others[5,7] in a modified form. These authors have given a valve of 0, 1, or 2 to the total score, making an evaluation for each of five previously indicated details. We, however, have retained our former method, taking into consideration different details and giving attention to the spatial configuration and to the clinical importance of the details. In the papers cited we give examples of more or less satisfactory agreement and the scores given in these cases.

TABLE I

SYSTEMS COMPARED	DIFFERENCE BETWEEN SCORES (FRONTAL-HORIZONTAL)	S.E. OF DIFFERENCE
BF	1.8	0.15
SF	1.2	0.13
BS	1.0	0.16

RESULTS

To draw conclusions from the scores mentioned above we calculated their averages and their standard errors.

The first question is whether there is a difference between the scores for normal subjects and those for patients. The normal subjects appear to score 0.3 higher than the patients, a result that is not significant since it varies much with the systems compared. Therefore, we calculated averages for all subjects,

normal subjects and patients together. In Fig. 1 the averages with their standard deviations are given for the three comparisons of the three systems, two by two, and for frontal and horizontal projections separately.

As has been shown in previous comparisons of different lead systems, here again the agreement between the frontal projections is much better than between the horizontal projections. The differences between the scores of the systems F, S, B (Frank, Schmitt, B_1W_4'') and their standard errors (S.E.) are shown in Table I. Without doubt these differences are a consequence of the fact that the linear dimensions of the heart in arterior-posterior direction is not a small fraction of the corresponding dimension of the trunk. Therefore, the evaluation of the component of the heart vector in this direction is subject to more error than that of its other components.

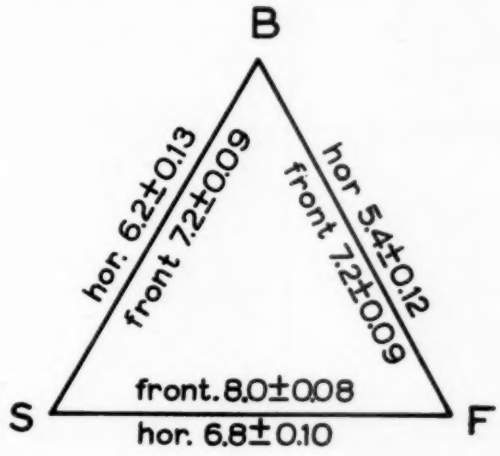

Fig. 1.—Correspondence two by two of frontal and horizontal projections of the three systems investigated, S,F,B, expressed by a score and its standard error.

It is obvious from Fig. 1 that the agreement between the Frank and Schmitt systems is significantly better than the agreement of either of them with our system B_1W_4''. Although this is a plea for these systems, it should be kept in mind that they are based on the same assumption, viz., that the trunk is equivalent to a homogeneous electrolyte. We, on the other hand, have reasons to assume that the conductivity of lung tissue is several times less than that of average human tissue, e.g., muscle tissue.[14] The discrepancy between our system and that of either Frank or Schmitt might be caused by a possible electrical heterogeneity of the human trunk.

Notwithstanding Frank's objection to the use of the left arm as an electrode[15] we have considered as paramount the advantage of using the extremities as electrodes. It is much easier and timesaving to apply an electrode to an extremity than to fix it to an exactly prescribed position on the trunk.

Another point to consider is the number of electrodes. It is obvious that we can expect a better result when a greater number of electrodes is used.

Looking at the results shown in Fig. 1 it is apparent that the agreement of the horizontal projections of the systems F and B is not satisfactory. A survey of all scores, as well as a detailed discussion of all vectorcardiograms on which this paper is based, indicate that the agreement in the majority of cases is satisfactory insofar as clinical use is concerned. However, the problem of the choice of a lead system has not yet been solved definitely. It must be hoped that it will be possible to find lead systems with essentially different positions of the electrodes which give practically identical vectorcardiograms.

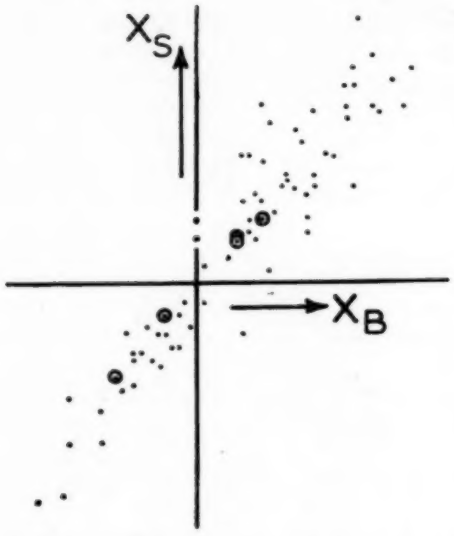

Fig. 2.—Correlation between the right-left components X_S and X_B of the heart vector in the system of Schmitt (S) and our own (B) for a part of all data. For this group of data the regression is expressed by $X_S = 1.2\ X_B$. A dot signifies a single point; an encircled dot signifies a double point.

Linear Relation Between the Two Lead Systems S and B.—It may be interesting to consider what causes a nonagreement of two lead systems. We must distinguish between individual and systematic effects. The first point will not be discussed here. As to systematic effects, there may be an inaccuracy of the factors with which the leads must be multiplied to find the components of the heart vector. These factors correspond to the lead-vector components in the simple case of four electrodes. They are the same for all subjects. In Frank's system they are represented by the network of resistances between subject and vectorcardiograph, while in Schmitt's system only equal factors occur.

A special and simple case of the relationship between two vectorcardiograms is the so-called linear transformation. This is a relationship between two vectorcardiograms or lead systems in which each of the three components of the heart vector in one system is a linear function of the three components in the other system. These three functions contain $3 \times 3 = 9$ numerical constants, the transformation coefficients. We shall not give the equations explicitly here but only mention some examples of a linear transformation. The simplest is that of identity, according to which each component in one system is equal to

the corresponding component in the other system. Examples of more complicated transformations are a rotation or a homogeneous dilatation in one or more directions. All this can be expressed algebraically with the 3×3 transformation coefficients.

A glance at the vectorcardiograms in the three lead systems shows that the individual discrepancies are preponderant, so that we cannot expect to be able to transform all vectorcardiograms of one lead system into those of another system by one and the same set of nine transformation coefficients. But even if the average transformation is only slight compared with the individual effects, it might be worth while to investigate its systematic effect. We have restricted this investigation to the comparison of the Schmitt system (S) and our own (B).

The transformation coefficients could be determined analytically, that is by calculation. But as we can expect the systematic effect to be found to be only a fraction of the random individual effect, we have used a much less accurate method, viz., a graphical one.

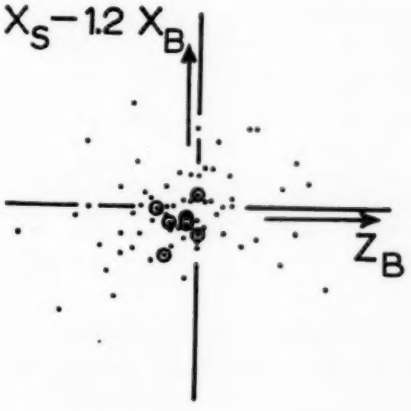

Fig. 3.—Correlation between the "error" $X_S - 1.2\ X_B$ and the anterior-posterior component Z_B. For this group of data the regression is expressed by $X_S - 1.2\ X_B = + 0.5\ Z_B$. A dot signifies a single point; an encircled dot signifies a double point.

Comparing two projections of a vectorcardiogram in the lead systems S and B respectively, we have chosen a few corresponding (synchronous) points on the loops. The coordinates of these points are measured and the six values for each point tabulated for all subjects. From these tables the coefficients have to be determined.

When the components of the heart vector are denoted by XYZ,* with an index S and B for the two lead systems, we have to evaluate the coefficients abc in the equation for the right-left component:

$$X_S = aX_B + bY_B + cZ_B$$

and in the two analogous equations for Y_S and Z_S. In an ideal case we could

*In our first paper (1946) on vectorcardiography we introduced the axes XYZ, that is, X was directed from right to left, Y was posterior-anterior, Z was head-foot. To prevent confusion we have adapted this paper to the American system: X = right-left, Y = head-foot, Z = anterior-posterior.

expect $a = 1$, $b = 0$, $c = 0$, so: $X_S = X_B$. To find out whether this is approximately true, the values of X_S and X_B for all subjects and for each subject for a few points on the loops are plotted. In Fig. 2 this is shown for a part of the total number of points.

The scattering of the points around a straight line through the origin of coordinates is due to different causes, among which are not only the inexactness of the linear transformation for each subject and the individual effects in different people but also the influence of the coefficients b and c not being zero.

The slope of the line gives the coefficient a, neglecting the influence of the terms bY_B and cZ_B. In Fig. 2 we have estimated the inclination by eye. This procedure, although not exact, is applied throughout this investigation to simplify the method. We read from the figure: $a = 1.2$, so $X_S = 1.2X_B$ or $X_S - 1.2X_B = 0$. For each point of Fig. 2, however, $X_S - 1.2X_B$ is not zero. The value of this "error" contains, apart from other contributions, the terms cZ_B and bY_B. A possible contribution of cZ_B can be found by plotting $X_S - 1.2X_B$ as an ordinate and Z_B as an abscissa (Fig. 3). Although the scattering is appreciable, we see by eye that there is a correlation. An approximate line gives:

$$X_S - 1.2X_B = + 0.5Z_B$$

or

$$X_S - 1.2X_B - 0.5Z_B = 0$$

Now the approximation can be continued by plotting $X_S - 1.2X_B - 0.5Z_B$ against Y_B. The inclination of the regression line (-0.1) gives the coefficient c. In this way we find:

$$X_S = 1.2X_B - 0.1Y_B + 0.5Z_B$$

It would be possible to start from this expression to find a second order approximation, but the systematic effect is so small compared with the random effects that we consider the last equation as the final one.

This procedure has been applied to the three components X_S, Y_S, Z_S and to all experimental points. After reducing the scale of S so that the average dimensions of the loops are the same in the two lead systems, we find the following linear transformation:

$$\begin{aligned} X_S &= + 1.0\,X_B - 0.1^5\,Y_B + 0.2^5\,Z_B \\ Y_S &= - 0.0^5\,X_B + 1.0\,Y_B - 0.1\,Z_B \\ Z_S &= - 0.2\,X_B + 0.6\,Y_B + 0.9\,Z_B \end{aligned}$$

From these equations, $X_BY_BZ_B$ can be solved and expressed in $X_SY_SZ_S$. The standard error of the coefficients is of the order of 0.1. This is, however, not an indication of great precision, because the random errors are much greater than the errors caused by the uncertainty of the coefficients of the linear transformation.

This transformation is not very far from identity since the three transformation coefficients in the diagonal are not far from unity, and five of the remaining coefficients are small. The main transformation effect is given by the coefficient 0.6 of Y_B in the third equation. This indicates that a footward loop is directed more posteriorly in the Schmitt system than in the B system.

A following point of the program could be to apply the linear transformation to the B system by using new adjustments of the potentiometers of the universal vectorcardiograph. In an ideal case the vectorcardiograms obtained in this way would be identical with the vectorcardiograms in the Schmitt system. The correspondence, however, cannot be expected to be so excellent; the only effect of the transformation would be to improve the scores given for the agreement of the transformed B and the S systems. This we have not done.

SUMMARY

The lead systems of Frank (F), Schmitt (S), and one of our own (B) are compared and the agreement is expressed by a score. On the whole, the agreement is satisfactory, but the anterior-posterior component of the heart vector is uncertain and spoils the correspondance, especially in comparing the F and B systems. A linear transformation is deduced to describe the average relation between the S and B systems.

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The Systolic I-J Acceleration-Force Values of 51 Normal Male Subjects From an Ultralow-Frequency Pendulum Ballistocardiographic System

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One method of evaluating the mechanical function of the heart with the least inconvenience to the subject is the ballistocardiogram. The employment of an ultralow-frequency[1] system with a calibrated acceleration-sensing transducer allows the determination of quantitative, though empirical, data. With this type of system the acceleration tracing gives the force information for all frequencies.[2] The curve as recorded represents the recoil record of the acceleration of the common center of gravity of the body incident to cardiac contraction and the flow of blood in the great vessels. Although the main acceleration systolic ejection complex[2] consists of the H-I and I-J strokes, most studies have been concerned with the amplitude of the I-J stroke. The most important contributions to the I-J upstroke[3] are initially a decrease in the rate of change in filling of the ascending aorta and aortic arch, and later a positive (increase) rate of change in filling of the thoracic and abdominal aorta.

For comparison to previously published values of the I-J stroke, this study is limited to the acceleration and calculated force values for this stroke from a pendulum ultralow-frequency system.

METHOD

The system used in this study has been described previously.[4] The natural frequency of the system was 0.5 per second, with a calculated F-1 of 0.2 per second, and an F-2 of 12.0 per second. The damping was weak, i.e., 0.28 critical.

The transducer was a calibrated differentiating coil-magnet velocity meter.[5a,b] The recorder was a single- or double-channel Sanborn direct-writing electrocardiograph.

All subjects were found to be normal by cardiac auscultation, blood pressure determination, and chest x-ray for cardiac size. They had not eaten or smoked for two hours prior to the recordings. Attainment of a basal state was not attempted, since prior observations had revealed deterioration of the ballistocardiogram with prolonged recumbency on the ballistic platform. Records were made during normal respiration, held expiration, and held inspiration. The room environment was air-conditioned (year-round), and the temperature was thermostatically controlled (78° F.).

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Direct measurements of the I-J stroke acceleration value (calibration, 1.0 millivolt output = 3.0 cm./sec.^{2}) were made on expiratory and inspiratory records of a stable pattern from complex to complex. The force value was calculated for expiration and inspiration by the classic formula,

$$F = \frac{M \cdot A}{G}$$

with all measurements in the centimeter-gram-second system. The force (F) was in grams, the body plus platform mass (M) in grams, the acceleration (A) in cm./sec.^{2}, and the gravitational constant (G) for this location[6] was 979.3 cm./sec.^{2}.

Complete subject and platform data with acceleration (cm./sec.^{2}) and force (grams) values are given in Table I. An acceleration record (expiration, *A-1;* and inspiration, *A-2*) for a normal subject is shown in Fig. 1.

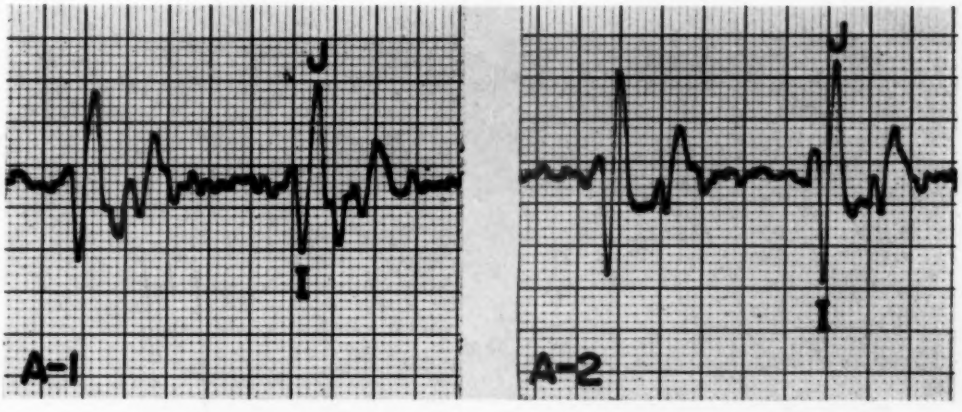

Fig. 1.—Acceleration record, *A-1* (expiration) and *A-2* (inspiration). Normal male subject, aged 23 years; weight 140 pounds; height 69.5 inches. Calibration: 11.0 small vertical chart spaces = 1 0 mv. = 3.0 cm./sec.^{2}. Expiration I-J = 20/11 × 3.0 = 5.45 cm./sec.^{2}, and inspiration I-J = 25/11 × 3.0 = 6.82 cm./sec.^{2}.

DISCUSSION

Fig. 2 shows the frequency distribution of subject data, with one standard deviation, for age (*A*, years), height (*B*, centimeters), body surface area (*C*, square meters), and body plus platform weight (*D*, kilograms). Fig. 3 shows the frequency distribution, with one standard deviation, of the expiratory I-J acceleration (*A*, cm./sec.^{2}) and calculated force (*B*, grams) values; the inspiratory I-J acceleration (*C*, cm./sec.^{2}) and calculated force (*D*, grams) values. Only 49 inspiratory values (*C* and *D*) are present because of unsatisfactory inspiratory tracings in two subjects.

There are few published data on quantitative acceleration measurements from ultralow-frequency systems to compare with the results herein. Scarborough and associates[7] give a value of 5.93 mg. for the mean I-J amplitude from a differential pendulum (25 male subjects, 20 to 29 years). Conversion (1.0 mg. = 0.98 c./sec.^{2}) gives a value of 5.81 cm./sec.^{2}.

Original studies[4] on 12 normal subjects from a ball-bearing platform gave an average (expiration plus inspiration/2) I-J acceleration value of 3.96 cm./sec.^{2}. This value on the same subjects from a Nickerson-type of spring ultralow-fre-

quency platform was 3.55 cm./sec.^{2}. These low acceleration values were undoubtedly related to the heavy platforms employed, with the consequent inertial impedance to acceleration. These studies[4] have now been extended to a larger number of subjects, with increased acceleration values from both systems.

The average (expiration plus inspiration/2) I-J acceleration value for the 51 subjects in the present study is 5.01 cm./sec.^{2}. This lower value, as contrasted to the value of Scarborough and associates,[7] is considered to be due to the larger platform weight (14.545 kilograms) and increased inertial impedance to acceleration, as contrasted to the lighter differential pendulum[7] (6.8 kilograms; i.e., less inertial impedance).

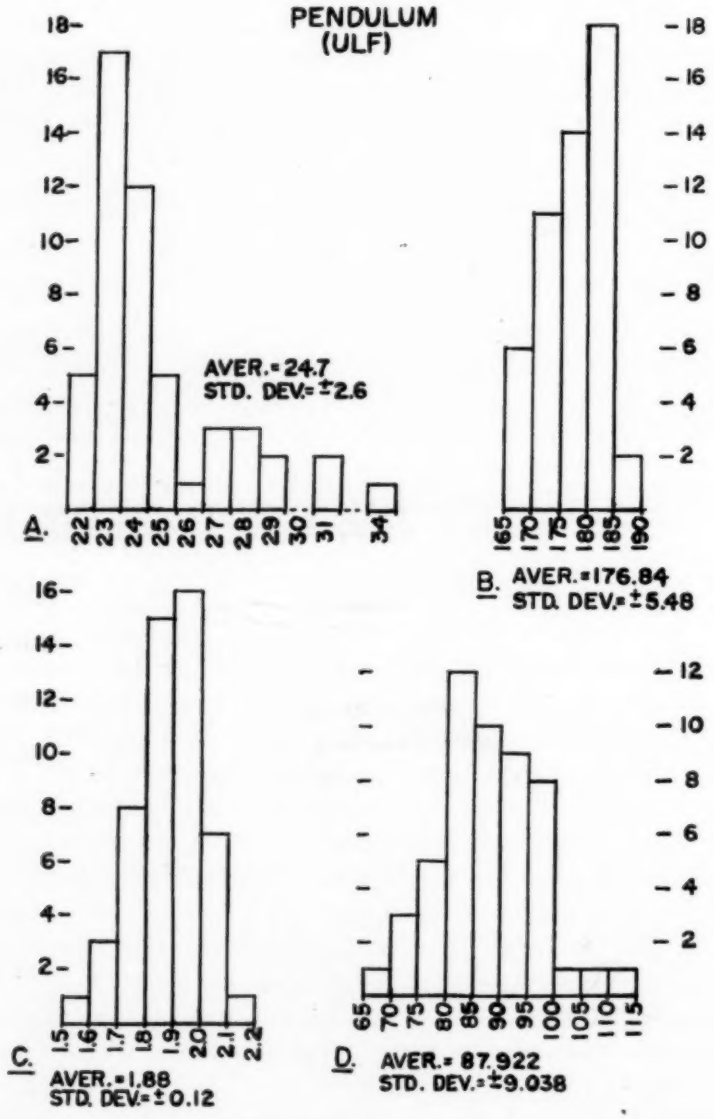

Fig. 2.—Bar-frequency diagrams showing number of subjects with average and one standard deviation for: *A*, age in years; *B*, height in centimeters (group units of 5.0 cm.); *C*, body surface area in square meters (group units of 0.1 sq. meter); *D*, combined weight factor, body plus platform, in kilograms (group units of 5.0 kilograms).

The average force value (expiration plus inspiration/2) for the 51 subjects in the present study is 435.24 grams. The mean I-J force from the differential pendulum of Scarborough and associates[7] is 485.8 grams. The same value from the ball-bearing platform[4] (12 subjects) is 344.09 grams, and from the Nickerson-type of spring ultralow-frequency platform[4] (12 subjects) it is 351.36 grams. Extension of these studies (ball-bearing and Nickerson-type ultralow-frequency systems) to a larger number of subjects has resulted in increased force values for both systems.

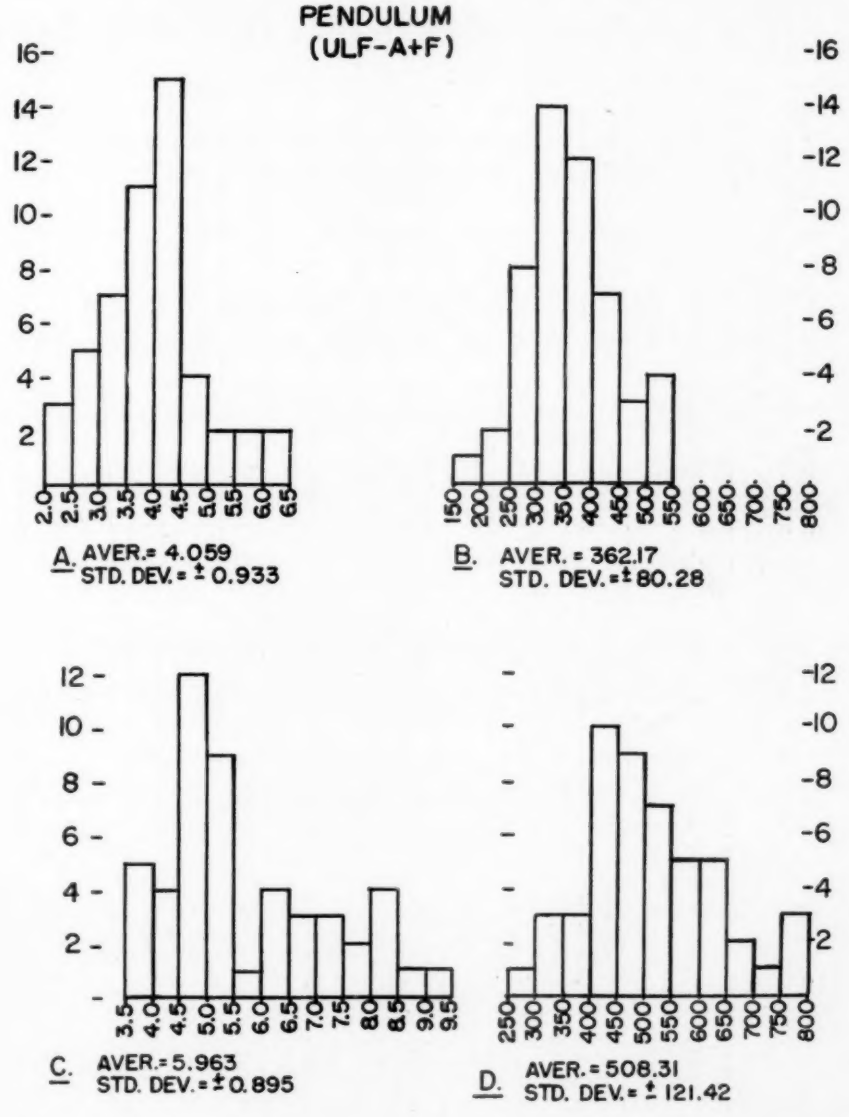

Fig. 3.—Bar-frequency diagrams showing number of subjects with average and one standard deviation for: *A*, expiratory I-J acceleration in group units of 0.5 cm./sec.^{2} (average, 4.059; standard deviation ± 0.933); *B*, expiratory I-J force in group units of 50 grams (362.17; ± 80.28); *C*, inspiratory I-J acceleration in group units of 0.5 cm./sec.^{2} (5.963; ± 0.895); and *D*, inspiratory I-J force in group units of 50 grams (508.31; ± 121.42).

TABLE I

SUBJECT AGE (YR.)	HEIGHT (CM.)	B.S.A. ($M.^2$)	SUBJECT WEIGHT (GRAMS $\times 10^3$)	PLATFORM WEIGHT (GRAMS $\times 10^3$)	SUBJECT + PLATFORM WEIGHT (GRAMS $\times 10^3$)	I-JA-Exp. ($CM./SEC.^2$)	I-JA-Exp. (FORCE-GRAMS)	I-JA-Insp. ($CM./SEC.^2$)	I-JA-Insp. (FORCE-GRAMS)
W.L. (23)	182.9	2.05	84.091	14.545	98.636	3.99	401.88	4.5	453.24
G.S. (25)	179.7	1.92	74.545	14.545	89.090	4.25	386.64	6.25	568.58
B. (22)	182.9	1.85	65.909	14.545	80.454	4.98	409.13	6.49	533.18
M.B. (28)	180.3	2.04	85.000	14.545	99.545	3.75	381.18	4.99	507.23
J.W. (29)	180.3	1.90	71.818	14.545	86.363	3.0	264.56	4.63	408.3
C. (27)	175.3	1.78	65.454	14.545	79.999	4.0	326.75	4.75	388.03
Bu. (23)	176.5	1.77	63.636	14.545	78.181	5.75	459.04	7.5	598.75
J.L. (24)	172	1.87	75.000	14.545	89.545	3.5	320.03	4.75	434.33
K.W. (25)	181.6	1.99	80.000	14.545	94.545	5.4	521.33	6.9	666.15
J.W.B. (25)	180.3	1.99	80.909	14.545	95.454	3.82	372.34	8.2	799.27
C.A. (24)	182.9	1.91	70.909	14.545	85.454	3.26	284.46	5.25	458.12
H.S.P. (23)	181.6	1.94	75.000	14.545	89.545	3.0	274.31	4.2	384.03
J.R. (23)	180.3	1.98	79.545	14.545	94.090	3.5	336.27	5.5	528.43
H.L. (23)	182.9	2.03	82.272	14.545	96.817	4.36	431.04	6.27	619.87
T.F. (23)	176.5	1.83	68.181	14.545	82.726	3.27	276.23	5.45	460.39
J.O.L. (23)	177.8	1.82	67.272	14.545	81.817	2.5	208.87	3.75	313.3
A.V. (23)	172.7	1.87	75.000	14.545	89.545	4.1	374.89	4.91	448.96

A.L.	(23)	185.4	1.89	68.181	14.545	82.726	4.08	344.65	5.18	437.58
E.T.	(24)	169	1.65	57.727	14.545	72.272	4.95	365.31	8.1	597.78
W.J.H.	(34)	165	1.54	50.909	14.545	65.454	4.5	300.76	7.05	471.2
J.A.R.	(25)	177	1.82	66.818	14.545	81.363	4.5	373.87	6.3	523.42
P.	(24)	172	2.08	96.818	14.545	111.363	3.0	341.15	3.6	409.38
L.P.	(22)	182	1.93	73.363	14.545	87.908	6.0	538.59	8.1	727.11
D.M.	(24)	180	2.03	85.000	14.545	99.545	4.35	442.17	5.1	518.41
R.C.	(31)	179	1.95	77.273	14.545	91.818	4.5	421.91	6.9	646.93
G.S.	(23)	173	1.84	71.818	14.545	86.363	3.6	317.48	3.9	343.93
R.T.	(24)	177.5	1.98	81.818	14.545	96.363	3.0	295.19	4.8	472.32
B.G.T.	(31)	170.6	1.82	72.045	14.545	86.590	4.05	358.1	7.35	649.89
J.C.F.	(24)	177.5	1.94	77.272	14.545	91.817	4.2	393.78	5.4	506.29
H.R.	(28)	185.4	2.05	79.091	14.545	93.636	4.37	417.84	5.5	525.88
A.D.M.	(29)	179	1.85	68.181	14.545	82.726	6.27	529.65	7.9	667.35
T.B.	(23)	169	1.68	60.454	14.545	74.999	4.5	344.63	8.1	620.33
C.	(25)	172.7	1.80	68.181	14.545	82.726	4.17	352.26	6.52	550.77
G.M.	(23)	182.9	1.82	63.636	14.545	78.181	3.47	277.02	4.26	340.09
Ra.	(22)	177.8	1.94	77.272	14.545	91.817	4.5	421.91	6.0	562.54
B.	(23)	180.3	2.02	84.091	14.545	98.636	4.8	483.46	——	——
W.R.	(24)	177.8	1.86	70.454	14.545	84.999	3.82	331.56	4.63	401.86
W.D.	(23)	181.6	1.99	79.545	14.545	94.090	3.25	312.26	5.00	480.39
S.J.	(24)	176.5	1.91	75.909	14.545	90.454	3.54	326.98	4.63	427.65

TABLE I—Cont'd

SUBJECT AGE (YR.)	HEIGHT (CM.)	B.S.A. ($M.^2$)	SUBJECT WEIGHT (GRAMS × 10^3)	PLATFORM WEIGHT (GRAMS × 10^3)	SUBJECT + PLATFORM WEIGHT (GRAMS × 10^3)	I-JA-Exp. (CM./$SEC.^2$)	I-JA-Exp. (FORCE-GRAMS)	I-JA-Insp. (CM./$SEC.^2$)	I-JA-Insp. (FORCE-GRAMS)
R.T. (23)	180.3	1.77	61.363	14.545	75.908	3.75	290.67	5.50	426.31
R.H. (23)	171.4	1.85	73.636	14.545	88.181	2.25	202.6	4.25	382.69
J.L.M. (23)	170.2	1.99	88.636	14.545	103.181	3.30	347.69	——	——
D.S.B. (22)	167.6	1.75	67.272	14.545	81.817	6.30	526.34	9.00	751.91
W.J.W. (24)	184.1	2.13	90.909	14.545	105.454	2.72	292.89	3.82	411.35
J.L.B. (27)	167.6	1.76	68.181	14.545	82.726	3.9	329.45	4.8	405.48
H.J. (26)	181.6	1.96	77.272	14.545	91.817	3.6	337.53	4.8	450.04
L.H. (22)	165.1	1.73	67.272	14.545	81.817	5.4	451.15	9.3	776.98
J.B.H. (27)	170.2	1.68	60.000	14.545	74.545	2.5	190.3	3.75	285.45
W.B. (28)	172.7	1.95	83.181	14.545	97.726	4.0	399.16	4.75	474.01
T.A. (24)	170.2	1.73	63.636	14.545	78.181	5.0	399.16	8.0	638.66
W.B. (24)	180.3	1.88	70.454	14.545	84.999	4.43	384.5	5.22	453.07
Average (24.7)	176.84	1.88	73.377	———	87.922	4.059	362.17	5.963	508.31
Standard Deviation (1) ±2.6	±5.48	±0.12	±9.038	———	±9.038	±0.933	±80.28	±0.895	±121.42

Values of individual subjects with average and one standard deviation for all factors (excepting platform weight): age-years (average 24.7; standard deviation ± 2.6); height (176.84 cm.; ± 5.48); body surface area (1.88 sq. meters; ± 0.12); subject weight (73.377 Kg.; ± 9.038); subject plus platform weight (87.922 Kg.; ± 9.038); I-J expiration (4.059 cm./$sec.^2$; ± 0.933); I-J expiration force (362.17 grams; ± 80.28); I-J inspiration (5.963 cm./$sec.^2$; ± 0.895); I-J inspiration force (508.31 grams; ± 121.42).

The average (4 subjects) I-J force from a pendulum ultralow-frequency system reported by Von Wittern[8] is 365 grams.

A comparative force value for healthy young male adults from a spring-type high-frequency platform (expiration plus inspiration/2) has been given by Starr[9] as 413 grams (range, 406 to 420 grams).

From these available data it appears that the differential pendulum[7] is the most efficient system described to date for obtaining the acceleration-force values of the ultralow-frequency ballistocardiogram. Although the results of the present study on 51 subjects exceed values from other ("spring HF" and ULF) systems for acceleration-force data, the acceleration and force values are 86.2 and 89.5 per cent, respectively, of the values from the differential pendulum.[7] This is considered to be due to a greater inertial impedance to acceleration as a result of a larger platform weight in comparison to the lighter differential pendulum.

SUMMARY

1. The acceleration-force values of 51 normal male subjects from an ultralow-frequency pendulum system have been given.

2. These values are greater than previously reported values, but are smaller than similar values from a differential pendulum.

3. These smaller values in relation to similar values from a differential pendulum are considered to be due to a greater inertial impedance to acceleration as a result of the heavier platform used in the present study.

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Observations on the Systolic I-J Stroke Acceleration-Force Values of 49 Male Subjects From a Roller Ball-Bearing Ballistocardiographic Bed

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Although ballistocardiography is of limited value in diagnosis, it is the only clinical method routinely applicable for a quantitative evaluation of the mechanical efficiency of the heart. The use of ultralow-frequency[1] systems and a calibrated transducer sensing acceleration allows calculation of the platform force. Although this value is empirical, and its relation to the actual internal heart force is unknown, the accumulation of normal standards (analogous to electrocardiography) will afford one way of assessing cardiac function.

Preliminary results obtained with the ball-bearing bed[2a-c] have been reported. Only recently[3] has this system been acknowledged as an ultralow-frequency system, with the reservation that "the acceleration (force) record derived therefrom is inferior." This was stated[2b] in 1956, but studies in progress using a lighter platform and a more refined accelerometer will be the subject of a future report.

METHOD

The dynamic characteristics[2a-c] of the ball-bearing bed have been given. The transducer was a differentiating bar-magnet velocity meter.[4a,b] The recorder was a Sanborn twin-channel direct-writing electrocardiograph. Recordings of acceleration were made during normal respiration, expiration, and inspiration. Measurements were made on expiratory and inspiratory tracings of a stable pattern from complex to complex.

All subjects were males having a normal cardiovascular evaluation by auscultation, blood pressure determination, and chest x-ray for heart size. All subjects had not eaten or smoked for two hours before the studies. Attainment of a basal state was not attempted, since early observations revealed deterioration of the ballistocardiogram after prolonged recumbency on the ballistic platform. The usual period of recumbency, before recording, was five minutes. The room environment was air-conditioned (year-round), and the temperature was thermostatically controlled (78° F.).

Complete subject and platform data with acceleration-force values are given in Table I. Normal acceleration records from two subjects are shown in Fig. 1.

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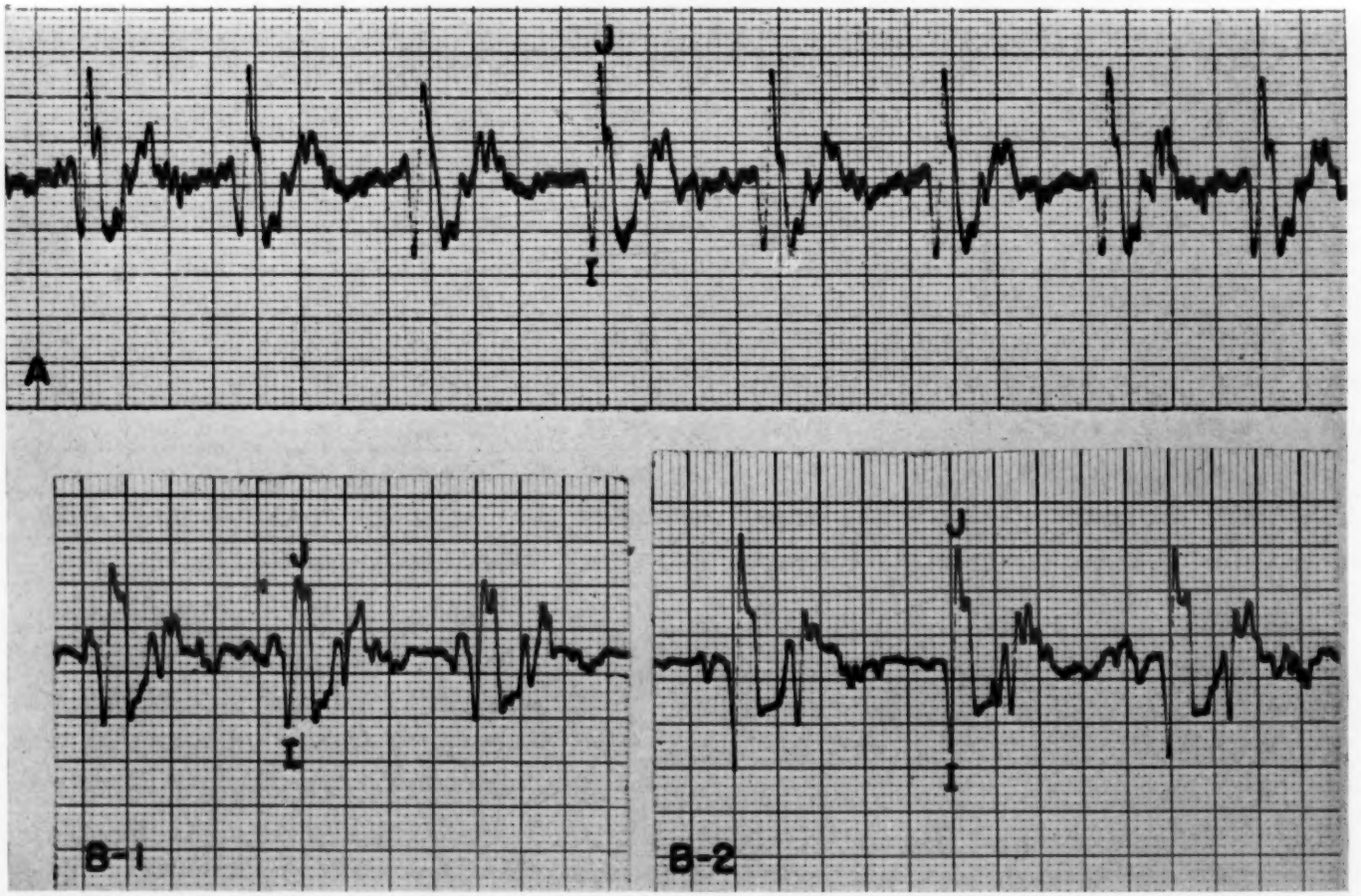

Fig. 1.—Acceleration records from two normal male subjects at graph speed of 25 mm./sec. (5.0 dark-line spaces across chart). *A*, Subject aged 25 years; height 68 inches, weight 154.5 pounds, normal respiration. Twelve small vertical chart spaces (millimeters) equal 30 mm./sec.^{2}. Five small vertical chart spaces equal one large (dark-line) vertical chart space. *B*, Subject aged 22 years; height 72 inches, weight 145 pounds. *B-1* = expiration; *B-2* = inspiration. Eleven and one-half small vertical chart spaces (millimeters) equal 30 mm./sec.^{2}.

TABLE I

SUBJECT AGE (YR.)	HEIGHT (CM.)	B.S.A. ($M.^2$)	SUBJECT WEIGHT (GRAMS $\times 10^3$)	PLATFORM WEIGHT (GRAMS $\times 10^3$)	SUBJECT + PLATFORM WEIGHT (GRAMS $\times 10^3$)	I-JA-Exp. ($CM./SEC.^2$)	I-JA-Exp. (FORCE-GRAMS)	I-JA-Insp. ($CM./SEC.^2$)	I-JA-Insp. (FORCE-GRAMS)
C.B.F. (32)	175.3	1.82	68.181	14.545	82.726	3.5	295.66	5.0	422.37
J.H. (25)	172.7	1.82	70.227	14.545	84.772	4.0	346.25	5.0	432.81
S.C. (25)	172.7	1.74	63.636	14.545	78.181	2.75	219.54	4.75	379.21
W.A.J. "Moose" (24)	198.1	2.22	88.636	14.545	103.181	5.25	553.15	8.0	842.89
J.B. (25)	180.3	1.85	68.181	14.545	82.726	2.61	220.48	6.0	506.84
C.S.F. (23)	180.3	2.08	88.636	14.545	103.181	2.57	270.78	3.42	360.33
Ri. (27)	179.1	1.85	68.181	14.545	82.726	2.46	207.81	3.54	299.04
E. (24)	168.9	1.68	60.000	14.545	74.545	3.43	261.09	5.79	440.74
D.B. (23)	182.9	1.91	71.363	14.545	85.908	5.0	438.61	6.0	526.34
T. (15)	174	1.78	66.136	14.545	80.681	4.9	403.69	7.36	606.36
L.C. (31)	182.2	2.02	82.272	14.545	96.817	4.75	469.6	5.75	568.46
V. (26)	195.6	2.37	106.818	14.545	121.363	2.75	340.8	3.75	464.73
D.L. (24)	174	1.81	68.181	14.545	82.726	3.0	253.42	4.72	398.72
A.S.D. (23)	174	1.80	67.272	14.545	81.817	3.75	313.3	4.75	396.84
W.L. (23)	182.9	2.05	84.091	14.545	98.636	3.5	352.52	3.99	401.88
G.S. (25)	179.7	1.92	74.545	14.545	89.090	4.64	422.12	7.09	644.99
B. (22)	182.9	1.85	65.909	14.545	80.454	4.25	349.16	6.24	512.64

M.B.	(28)	180.3	2.04	85.000	14.545	99.545	3.5	355.77	4.98	506.2
J.W.	(29)	180.3	1.90	71.818	14.545	86.363	3.0	264.56	4.25	374.8
C.	(27)	175.3	1.78	65.454	14.545	79.999	3.62	295.72	6.5	530.98
Bre.	(23)	176.5	1.77	63.636	14.545	78.181	4.75	379.21	6.0	479
J.L.	(24)	172	1.87	75.000	14.545	89.545	4.5	411.47	6.0	548.62
K.W.	(25)	181.6	1.99	80.000	14.545	94.545	5.45	526.16	7.1	685.46
J.W.B.	(25)	180.3	1.99	80.909	14.545	95.454	4.36	424.98	6.27	611.15
Ca.	(24)	182.9	1.91	70.909	14.545	85.454	2.72	237.35	5.0	436.3
H.S.P.	(23)	181.6	1.94	75.000	14.545	89.545	2.72	248.71	5.18	473.65
J.R.	(23)	180.3	1.98	79.545	14.545	94.090	3.28	315.14	4.36	418.9
H.L.	(23)	182.9	2.03	82.272	14.545	96.817	4.08	403.36	5.73	566.49
T.F.	(23)	176.5	1.83	68.181	14.545	82.726	2.18	184.15	4.9	413.93
J.O.L.	(23)	177.8	1.82	67.272	14.545	81.817	2.72	227.25	4.36	364.26
A.V.	(23)	172.7	1.87	75.000	14.545	89.545	3.0	274.31	4.25	388.61
A.L.	(23)	185.4	1.89	68.181	14.545	82.726	4.08	344.66	4.63	391.12
E.T.	(24)	169	1.65	57.727	14.545	72.272	4.2	309.96	5.1	376.38
W.J.H.	(34)	165	1.54	50.909	14.545	65.454	2.4	160.41	4.2	280.72
P.	(24)	172	2.08	96.818	14.545	111.363	2.4	272.92	——	——
L.P.	(22)	182	1.93	73.363	14.545	87.908	4.2	377.02	——	——
D.M.	(24)	180	2.03	85.000	14.545	99.545	2.4	243.95	3.75	381.18
R.C.	(31)	179	1.95	77.273	14.545	91.818	3.3	309.4	4.2	393.79

TABLE I—Cont'd

SUBJECT AGE (YR.)	HEIGHT (CM.)	B.S.A. ($M.^2$)	SUBJECT WEIGHT (GRAMS $\times 10^3$)	PLATFORM WEIGHT (GRAMS $\times 10^3$)	SUBJECT + PLATFORM WEIGHT (GRAMS $\times 10^3$)	I-JA-Exp. ($CM./SEC.^2$)	I-JA-Exp. (FORCE-GRAMS)	I-JA-Insp. ($CM./SEC.^2$)	I-JA-Insp. (FORCE-GRAMS)
G.S. (23)	173	1.84	71.818	14.545	86.363	3.3	291.02	3.9	343.94
R. T. (24)	177.5	1.98	81.818	14.545	96.363	2.4	236.16	3.9	383.76
B.G.T. (31)	170.6	1.82	72.045	14.545	86.590	4.2	371.36	5.1	450.94
J.C.F. (24)	177.5	1.94	77.272	14.545	91.817	3.9	365.65	5.1	478.16
H.R. (28)	185.4	2.05	79.091	14.545	93.636	3.75	358.55	5.5	525.88
A.D.M. (29)	179	1.85	68.181	14.545	82.726	4.71	397.88	6.64	560.91
T.B. (23)	169	1.68	60.454	14.545	74.999	5.75	440.36	6.87	526.13
C. (25)	172.7	1.80	68.181	14.545	82.726	3.65	308.33	5.48	462.92
G.M. (23)	182.9	1.82	63.636	14.545	78.181	3.5	279.42	5.4	431.1
Ra. (22)	177.8	1.94	77.272	14.545	91.817	5.1	478.16	——	——
B. (23)	180.3	2.02	84.091	14.545	98.636	3.2	322.31	4.2	423.03
Average (24.8)	178.3	1.90	73.783	——	88.328	3.66	329.26	5.22	465.51
Standard Deviation (1) (±3.22)	±6.15	±0.14	±10.154	——	±10.154	±0.93	±87.55	±1.10	±105.38

Values of individual subjects with average and one standard deviation for all factors (excepting platform weight): age-years (average, 24.8; standard deviation ±3.22); height (178.3 cm.; ± 6.15); B. S. A. (1.90 sq. meters; ± 0.14); subject weight (73.783 Kg.; ± 10.154); subject plus platform weight (88.328 Kg.; ± 10.154); I-J expiration (3.66 cm./sec.^{2}; ± 0.93); I-J expiration force (329.26 grams; ± 87.55); I-J inspiration (5.22 cm./sec.^{2}; ± 1.10); I-J inspiration force (465.51 grams; ± 105.38).

The acceleration values were obtained from direct chart measurements (calibrated amplitude, 3.0 cm./sec.^{2} per millivolt output), and the force values were calculated in grams by use of the classic formula,

$$F = \frac{M \cdot A}{G}$$

with all measurements in the centimeter-gram-second system. The mass (M) is the sum of the body plus platform, and the acceleration (A) is the measured I-J value. The gravitational constant (G) for this geographic location[5] is 979.3 cm./sec.^{2}.

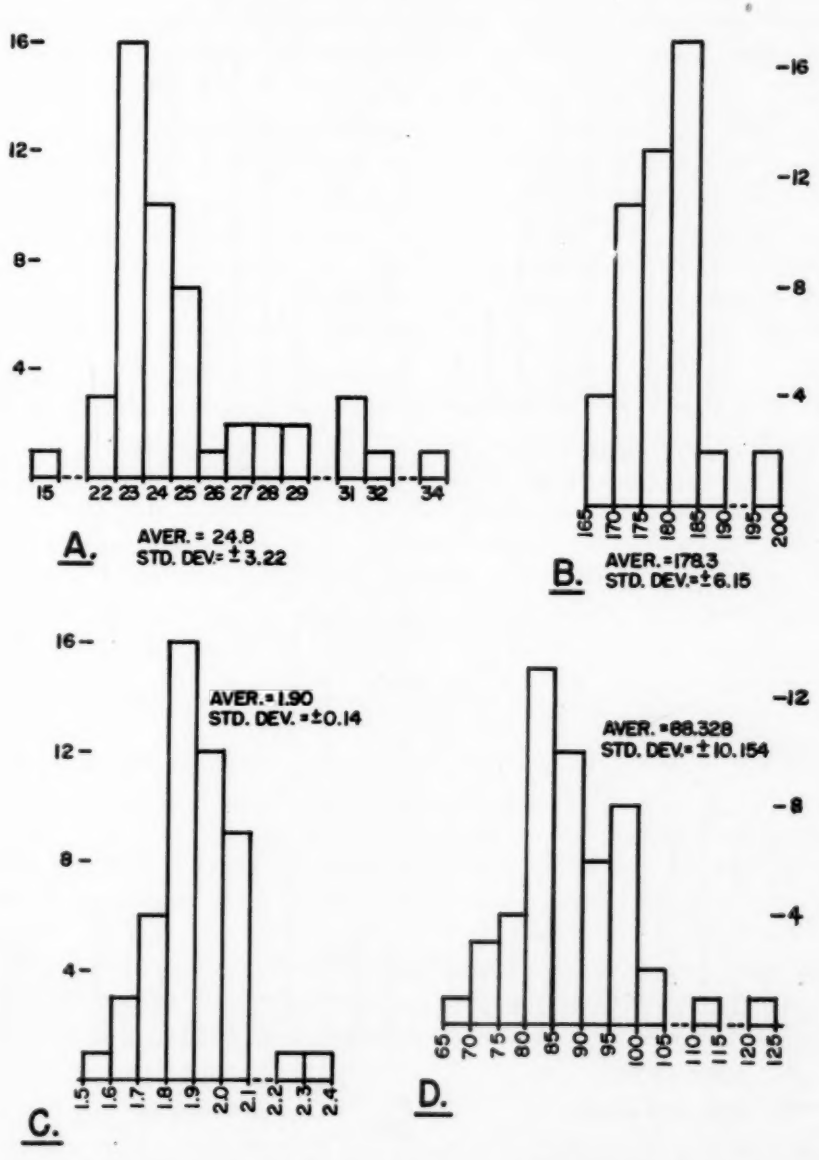

Fig. 2.—Bar-frequency diagrams showing number of subjects with average and one standard deviation for: *A*, age in years; *B*, height in centimeters (group units of 5 centimeters); *C*, body surface area in square meters (group units of 0.1 sq. meter); and *D*, combined weight factor, body plus platform, in kilograms (group units of 5 kilograms).

DISCUSSION

Fig. 2 shows the frequency distribution of subject data, with one standard deviation, for age (*A*, years), height (*B*, centimeters), body surface area (*C*, square meters), and body plus platform weight (*D*, kilograms). Fig. 3 shows the frequency distribution, with one standard deviation, of the expiratory I-J acceleration (*A*, centimeters/sec.^{2}) and calculated expiratory force (*B*, grams); and the inspiratory I-J acceleration (*C*, centimeters/sec.^{2}) and calculated inspiratory force (*D*, grams). There are only 46 inspiratory values (*C* and *D*) because of unsatisfactory tracings in three subjects (held inspiration with Valsalva effect).

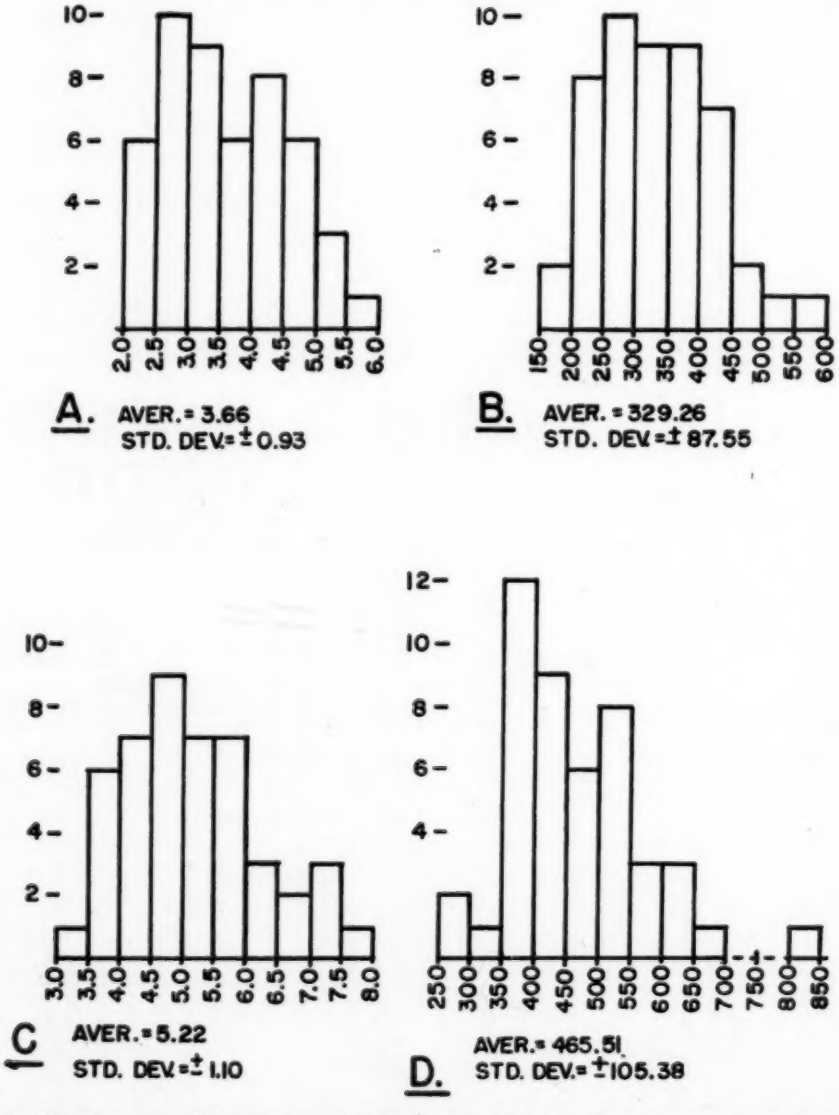

Fig. 3.—Bar-frequency diagrams showing number of subjects with average and one standard deviation for: *A*, expiratory I-J acceleration (cm./sec.^{2}) in group units of 0.5 cm./sec.^{2} (average 3.66; standard deviation ± 0.93); *B*, expiratory I-J force (grams) in group units of 50 grams (329.26; ± 87.55); *C*, inspiratory I-J acceleration (cm./sec.^{2}) in group units of 0.5 cm./sec.^{2} (5.22; ± 1.10); and *D*, inspiratory I-J force (grams) in group units of 50 grams (465.51; ± 105.38).

Attempted correlation of the expiratory and inspiratory acceleration-force values with subject factors of height, weight, and body surface area, as well as the combined weight factor (body plus platform), yielded insignificant linear results.

It is to be noted also that the overlap (one standard deviation) of the expiratory and inspiratory values amounts to 25 per cent of the expiratory range and 21 per cent of the inspiratory range of values. Similar overlap relationships (one standard deviation) for the range of expiratory and inspiratory force values amounts to 32 and 22 per cent, respectively. These results indicate the limitation of attempting to establish too rigid criteria for normal acceleration-force values, and suggest that grading[6] of the ballistocardiogram (I-IV) on an empirical basis would give additional help in evaluating a tracing.

The average of the sum of the expiratory (average, 329.26) and inspiratory (average, 465.51) force values from the ball-bearing system is 397.38 grams. The average I-J force value (expiration plus inspiration/2) for normal young adult males from the Starr[7] high-frequency platform is 413 grams (range, 406 to 420 grams). This average value for four normal subjects from a pendulum ultralow-frequency system[8] is 365 grams. This value from an ultralow-frequency differential pendulum[9] platform (25 normal males, 20 to 29 years old) has been given as 485.8 grams (mean I-J).

The result (I-J force-average) for the ball-bearing platform is nearly equal (96 per cent) to that of the Starr system, but significantly smaller (82 per cent) than the differential pendulum mean I-J force value. Studies are now under way with a ball-bearing platform (7.7 kilograms) nearly equal to the weight of the differential[9] pendulum system (6.8 kilograms). Improved results in comparison to the differential pendulum system are expected, since the values reported herein were obtained with a ball-bearing platform weighing approximately 14.5 kilograms.

SUMMARY

1. The systolic I-J stroke acceleration-force values from a ball-bearing ballistic platform have been determined for 49 normal males.

2. The wide range and overlap of expiratory and inspiratory acceleration-force values preclude the establishment of a too rigid range of quantitative values, and indicate the need for qualitative (Grade I-IV) evaluation of the ballistocardiogram.

3. The force value obtained with the ball-bearing system is nearly equal to the result from the Starr high-frequency system, but is only 82 per cent of the force value from a differential pendulum.

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The Effect of Pentolinium Tartrate (Ansolysen) on Blood Pressure in Terminal Vessels and on Capillary Diameter

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The clinical method of measuring "capillary" pressure described by Davis[1] has become a routine examination in our hands. Since this method is better described as a method for measuring the blood pressure in the terminal digital vessels, "terminal vessel pressure" will be referred to in this paper.

In ten patients with severe hypertension who were treated with Ansolysen (pentolinium tartrate) the terminal vessel pressure was measured repeatedly, and the effect of Ansolysen on brachial artery and terminal vessel blood pressure and on capillary diameter was studied.

MATERIAL AND METHODS

Of the 10 patients investigated 6 were males and 4 were females. Nine ranged in age from 43 to 56 years and suffered from essential hypertension. In one patient, aged 70 (L., Table I), hypertension complicated diabetes mellitus. All 10 had severe cardiovascular complications. In these 10 patients brachial blood pressure, pressure in the terminal digital vessels, and diameter of the capillaries in the nail beds and conjunctivae were determined before treatment with Ansolysen. The lowest oral effective dose of Ansolysen was determined for each patient individually by measuring the blood pressure half-hourly after each dose and gradually increasing the dose daily until an effective response was obtained (Table I). Ansolysen was given two or three times daily.

Capillary diameter and terminal vessel pressure were measured at the time that the Ansolysen had its maximal effect. This was usually 4 hours after its administration.

Patients continued treatment with the drug and returned for periodic examination and assessment, daily at first, then weekly, later at two-weekly and three-weekly intervals, and, when their condition was stable, at monthly intervals. On each visit brachial blood pressure was measured half-hourly from 2 to 6 hours after Ansolysen was administered. Terminal vessel pressure and capillary diameter were measured at the time of the maximum fall in blood pressure on each visit.

The technique of measuring terminal vessel blood pressure has been fully described.[1] The principle of the method is to fasten a cuff attached to a sphygmomanometer around the adjacent parts of the second and third phalanges of the finger. The pressure is raised in the cuff until blood flow is no longer seen in the capillaries of the nail bed, which is examined through a microscope at a magnification of 60. The cuff pressure is then lowered until normal flow is seen in the capillaries, and this pressure is regarded as terminal vessel pressure.

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The diameter of the lumen of the capillaries was measured in terms of an ocular scale in which the actual distance represented between divisions and the actual width represented by a line between the divisions had been measured.[2] The capillary diameter was usually nearly constant when an effective maintenance dose of Ansolysen was being taken.

Ansolysen has been given to 7 patients for 15 to 33 months, to 1 patient for 9 months, and to 1 patient for 6 months, while in Patient Ba (Table I) administration had to be terminated after 1 month (see below).

TABLE I. BLOOD PRESSURE AND TERMINAL DIGITAL VESSEL PRESSURE (IN MM. HG) BEFORE AND AFTER ANSOLYSEN

PATIENT	DAILY DOSE (MG.)	BLOOD PRESSURE		TERMINAL VESSEL PRESSURE	
		BEFORE	AFTER	BEFORE	AFTER
S.	90	250/125	160/90	50	35
R.	140	225/140	140/100	55	30
H.	230	190/130	165/105	55	35
B.	100	220/130	180/100	70	40
Y.	240	250/140	150/90	50	25
L.	120	250/130	170/100	55	35
F.	580	210/120	130/100	70	35
A.	200	200/140	160/110	80	50
C.	130	200/130	135/90	45	25
Ba.	130	235/145	170/115	60	50

RESULTS

In 70 per cent of patients with normal blood pressure the terminal vessel pressure is less than 25 mm. Hg, and in 90 per cent the terminal vessel pressure is less than 45 mm. Hg.

In 100 patients with essential hypertension followed up for 2 to 6 years[3] the terminal vessel pressure was 45 mm. Hg or more in 55. In severe hypertension the terminal vessel pressure is usually 45 mm. Hg or more.[2] In the ten patients described here the terminal vessel pressure was 45 to 60 mm. Hg in seven, and 70 to 80 mm. Hg in three, before treatment with Ansolysen. Upon institution of treatment with Ansolysen the terminal vessel pressure did not fall until the dose was sufficient to produce an appreciable fall in brachial blood pressure. When the effective dose of Ansolysen was found, terminal vessel pressure fell and remained low and nearly constant as long as effective doses of Ansolysen were being taken. Treatment with Ansolysen resulted in terminal vessel pressures of 50 mm. Hg in two, 30 to 40 mm. Hg in six, and 25 mm. Hg in two (Table I).

Normal capillaries had a diameter[2] ranging from 5 to 12 μ, moderately thin capillaries had a diameter of 3.5 to 5.0 μ, and very thin capillaries had a diameter of less than 3.5 μ. Before treatment with Ansolysen the conjunctival capillaries were very thin in seven patients, thin in two, and normal in one. With Ansolysen the conjunctival capillaries dilated appreciably in eight of the nine patients who had thinning of the capillaries. Moderately thin capillaries became normal in diameter, and very thin capillaries became moderately thin. After Ansolysen

there was an appreciable dilatation in the nail-bed capillaries of seven of the nine patients in whom the capillaries had been narrow previously. Capillaries of normal diameter dilated further after Ansolysen.

Two patients (B. and L.) whose blood pressure had been much reduced while they were on Ansolysen, gave up Ansolysen of their own volition at a period when they felt better and believed that there was no need to continue. However, the blood pressure rose and the terminal vessel pressure and capillary diameter returned to the levels present before treatment. When these patients resumed taking Ansolysen, the terminal vessel pressure fell and the lumen of the capillaries dilated to the same values as previously. In Patient Ba when the blood pressure fell from 235/145 to 170/115 mm. Hg after Ansolysen, severe retrosternal pain always occurred, and although no further deterioration was seen in his already pathologic electrocardiogram, Ansolysen treatment was abandoned.

DISCUSSION

A critical consideration of the method of measuring "capillary" (terminal vessel) pressure was given in previous reports.[1,2] A terminal vessel pressure of 45 mm. Hg by this method is considered high. It is necessary to consider whether the method really records digital arterial pressure, as suggested by P.S. Rhoads (personal communication), or arteriolar pressure or capillary pressure, as discussed by Landau and Davis.[2] The end point in the measurement is the pressure at which return of normal blood flow in a group of the nail-bed capillaries is seen, after the capillary flow has been obliterated previously by increasing the pressure in a cuff over the second and third phalanges. The normal range of pressure by this method was the same as that found by Landis[4] using a microcannula inserted in the capillaries, so that it is tempting to regard the method as a measure of capillary pressure. There is a high correlation between increased "capillary" pressure and capillary thinning. It may be that the results obtained by Landis and by Davis reflect arteriolar pressure rather than capillary pressure. The results of both methods may be modified by nearby arteriovenous anastomoses.[5] Boas and Mufson[6] have suggested that in certain conditions the capillary resistance may be so increased as to bring capillary pressure close to arteriolar pressure. The blood pressure in the digital arteries[7] is 101±, a standard deviation of 13 mm. Hg, values considerably higher than those given by our method. It is therefore unlikely that our method measures digital arterial pressure. The practical application is the same whether the method measures capillary pressure or arteriolar or digital arterial pressure. In view of the foregoing, however, the method is better referred to as a method for measuring the blood pressure in the terminal digital vessels.

The results showed that Ansolysen reduced terminal vessel pressure substantially. In eight out of ten patients the terminal vessel pressures were reduced to normal level. In two patients the pressure, although reduced, was still high.

Capillary diameter was usually reduced in severe hypertension. Ansolysen usually produced appreciable capillary dilatation when an effective maintenance

dose was being taken. This action is in keeping with a ganglionic blocking effect on sympathetic vasomotor tone.

There is evidence[3] that those patients with hypertension who have high terminal vessel pressure or severe thinning of the capillaries are liable to have a bad prognosis. Of 300 patients with hypertension who were followed up for 2 to 6 years, eight died. Seven of these eight patients had high terminal vessel pressure or severe thinning of the capillaries, or both. Since publication of this series, two more patients have died. Both had thinning of the capillaries and high terminal vessel blood pressure. Those patients with hypertension whose terminal vessel pressure was normal, and in whom capillary diameter was either normal or only moderately reduced, were usually the less adversely affected by their hypertension.

Ansolysen reduced the pressure in the terminal vessels and increased the capillary diameter to values which are associated with a relatively good clinical state. Indeed, Ansolysen had improved appreciably the clinical condition of seven of the ten patients under review.

SUMMARY

Ten patients with severe hypertension were treated with oral pentolinium tartrate (Ansolysen).

Before treatment the blood pressure in the terminal digital vessels was high in all patients, and the diameter of the capillaries in the conjunctivae and nail beds was reduced in most.

When effective therapeutic doses of Ansolysen were given, the terminal vessel pressure was reduced in all and became normal in eight patients. Also, the diameter of the capillaries increased appreciably in nearly all the patients.

The values of terminal vessel pressure and capillary diameter in these severe cases after treatment with Ansolysen were similar to those found in a group of hypertensive patients whose clinical state was relatively good.

We wish to express our appreciation to M. Ivry for skilled observations and help.

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The Spatial Vectorcardiogram of Patients With Malignant Neoplasms

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The relationship of the spatial vectorcardiogram and electrocardiogram to the clinical data and postmortem findings in the heart has been studied for the past few years at the New Orleans Veterans Administration Hospital. Of 160 patients who were followed to necropsy, 89 had malignant neoplasms (excluding the lymphomata and the leukemias). The 22 patients of this group in whom the malignant neoplasms were associated with myocardial infarction have been reported in detail elsewhere.[1] This report is concerned with an investigation of the characteristics of the spatial vectorcardiogram (sVCG) and the electrocardiogram (ECG) and their relationship to autopsy findings in patients with malignant neoplasms.

MATERIAL AND METHODS

The electrocardiographic study included standard leads V_R, V_L, V_F, and V_1-V_6, recorded with a string galvanometer. The spatial vectorcardiograms were obtained as previously described,[2] with the equilateral tetrahedron as the reference frame. These were recorded several days to weeks prior to death. Wire loop models of the sVCG were constructed for each subject. Following the initial routine pathologic studies of the heart, the ventricles were measured for thickness and weighed separately.[1]

Because of the possible influence upon the pulmonary circulation and the right side of the heart, the group of 30 patients with bronchogenic carcinoma were analyzed separately from the 38 patients with other primary visceral malignant neoplasms.

Tentative criteria for right and left ventricular hypertrophy similar to those in a previous study[1] were adopted: right ventricular hypertrophy was assumed when the right ventricular thickness exceeded 5 mm.[4] or the weight of the right ventricle exceeded 50 grams; left ventricular hypertrophy was assumed when the left ventricular thickness exceeded 15 mm.[4] or the weight of the left ventricle exceeded 170 grams.

RESULTS

The electrocardiogram was considered to manifest changes typical of right ventricular hypertrophy in 8 patients (Tables I, II, and III). The spatial vector-

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TABLE I BRONCHOGENIC CARCINOMA (38)

PATIENT NUMBER*	AGE (YR.)	QRSsÊ LOOP					ECG	CARDIAC STUDY								
		TYPE	DISTORTION	POSITION	PATTERN	TS		HEART WEIGHT (GM.)			LV/RV RATIO	THICKNESS (MM.)		CORONARY ARTERY ATHEROSCLEROSIS	MUSCLE	
								TOTAL	RV	LV		RV	LV		BROWN	METAST
1.	40	1	+	V	NS	+	Normal	273	55	129	2.34	6	12			
2.	65	1	+	V	NS		Normal	197	42	93	2.21	4	12	P	+	
3.	57	1	+	V	NS	+	Abnormal T waves	352	—	—	——	5	13	P		
4.	50	1	+	V	NS	+	Normal	256	29	128	4.41	4	13		+	
5.	69	1	+	V	NS	+	Normal	190	—	—	——	6	14	P	+	
6.	60	1	+	V	NS	+	Early RVH	270	50	144	2.88	5	15			
7.	61	1	+	V	RVH		RVH	233	34	97	2.85	5	11	P	+	
8.	58	1	‡	V	NS	+	Normal	204	27	86	3.19	3	12	P		
9.	60	1	‡	V	NS	+	Abnormal T waves	264	—	—	——	5	15	P		
10.	53	1	+	V	NS	+	Normal	226	33	132	4.00	3	14	P		
11.	60	Trans.	+	—	Lateral wall scar		Abnormal T waves	246	—	—	——	3	9	P		+
12.	64	1	+	V	NS	+	Normal	181	29	102	3.51	3	13	P	+	
13.	58	Trans.	+	—	RVH	+	RVH	405	65	159	2.45	5	20	P		
14.	44	1	+	V	NS		Normal	262	35	139	3.97	5	15			+
15.	68	1	+	—	LVH or diaphragmatic infarct		Diaphragmatic wall infarct	240	36	12	3.36	4	15	P	+	

16.	33	1	+	V	Possible posterior infarct		Abnormal T waves	262	—	—	——	3	12		+	
17.	62	1	+	V	NS		Normal	215	—	—	——	4	15	P		
18.	61	1	+	V	NS	+	Normal	226	34	122	3.60	3	13	P		+
19.	56	2	+	V	NS		Normal	205	35	115	3.29	4	13		+	
20.	62	Trans.	+	—	LVH and lateral infarct		LVH; lateral infarct	267	36	121	3.36	5	16			+
21.	60	1	+	V	Possible posterolateral scar	+	RVH; abnormal T	245	—	—	——	-	—			
22.	63	1	+	—	NS		LVH	424	45	279	6.20	4	18			
23.	64	Trans.	+	—	Possible diaphragmatic infarct	+	Normal (possible RVD)	406	77	126	1.80	4	13	P		
24.	39	1	+	V	NS	+	Pericarditis; abnormal T wave	290	—	—	——	-	—			
25.	84	-	‡	—	RBBB		RBBB with Rad.	246	38	117	4.41	3	13	P	+	
26.	67	-	+	—	Posterior infarct	+	Posterior infarct	314	52	122	2.26	3	12		+	+
27.	65	1	+	V	Posterior and anteroseptal infarct	+	RVH with Rad. vs. Postero-anteroseptal infarct	359	—	—	——	6	—			
28.	59	Trans.	+	—	NS		Normal	263	48	133	2.83	3	15	P		
29.	60	-	+	—	Possible posterior infarct		Normal	290	64	163	2.54	5	13	P		
30.	37	1	+	V	Possible posterior infarct		Abnormal T waves	218	37	139	3.76	5	14	P	+	
31.	53	1	+	V	Possible posterior infarct		RBBB delay	225	38	99	2.60	3	12	P		
32.	60	-	+	—	Possible posterior infarct; RBBB		Possible posterior infarct—RBBB	300	50	112	2.24	3	12	P		+
33.	74	-	+	—	Lateral basal infarct and LVH		Possible lateral infarct—LVH	229	34	129	3.79	3	11		+	
34.	78	1	+	V	NS		Normal	331	37	142	3.83	4	14	P		+
35.	60	-	+	—	Posterolateral infarct		Loss of septal Q	240	27	118	4.37	3	20	P		
36.	61	1	+	V	NS		Lateral infarct	266	—	—	——	5	14			
37.	61	1	+	V	NS		Normal	230	44	134	3.04	4	15	P		
38.	41	2	+	V	NS		Normal	192	28	108	3.86	3	12	P		

*Numbers 1 through 28 are uncomplicated cases. Numbers 29 through 38 are cases associated with myocardial infarction.

TABLE II. OTHER MALIGNANT NEOPLASMS (51)

PATIENT NUMBER*	AGE (YR.)	PRIMARY SITE	QRSsÊ LOOP					ECG	CARDIAC STUDY								
			TYPE	DISTORTION	POSITION	PATTERN	TS		HEART WEIGHT (GM.)			LV/RV RATIO	THICKNESS (MM.)		CORONARY ARTERY ATHEROSCLEROSIS	MUSCLE	
									TOTAL	RV	LV		RV	LV		BROWN	METAST
39.	49	Stomach	1	0	V	NS	+	Normal	177	—	—	——	3	9		+	
40.	48	Rectum	1	+	V	NS	+	Abnormal T waves	200	30	85	2.83	2	11	P	+	
41.	35	Brain	1	‡	V	N		Normal	320	—	—	——	4	13	P		
42.	59	Colon	1	+	—	NS	+	Normal	243	—	—	——	3	13	P	+	
43.	35	Ampulla of Vater	2	+	V	NS		Abnormal T waves	287	39	139	3.56	3	13			
44.	59	Esophagus	1	+	V	NS	+	Abnormal T waves	275	41	138	3.36	5	15	P		+
45.	45	Rectum	1	+	H	NS		Abnormal T waves	230	31	116	3.74	4	9		+	
46.	46	Stomach	2	+	H	NS		Abnormal T waves	241	34	134	3.94	2	13	P	+	
47.	62	Pancreas	2	+	V	NS	+	Normal	179	24	78	3.25	4	10	P	+	
48.	47	Pancreas	2	+	V	Possible basal scar		Normal	263	—	—	——	3	13			
49.	65	Tongue	Trans.	+	H	RVH		RVH	291	51	142	2.78	5	14	P		
50.	61	Colon	1	+	V	RBBB		RBBB	178	30	99	3.30	4	11	P	+	
51.	67	Pharynx	1	+	V	NS		Abnormal T waves	200	—	—	——	–	—		+	
52.	62	Kidney	–	+	H	LVH		Normal	317	36	154	4.27	5	15	P		
53.	45	Liver	1	+	V	NS		Normal	194	34	126	3.90	4	15		+	
54.	34	Penis	1	+	V	NS	+	Normal	240	—	—	——	4	15			
55.	64	Kidney	2	+	H	RVH		RVH	355	38	145	3.81	8	17			
56.	58	Stomach	1	+	H	NS		Abnormal T waves	270	—	—	——	3	16	P		
57.	60	Stomach	1	+	V	NS	+	LVH	329	46	148	3.22	4	15	P		
58.	58	Kidney	–	+	V	LBBB		LBBB	328	42	229	5.45	3	17			+
59.	38	Brain	1	+	H	NS		Normal	247	—	—	——	4	9			
60.	65	Tongue	–	+	V	LBBB		LBBB	324	40	177	4.42	4	15	P		+
61.	60	Colon	1	+	—	NS		Abnormal T waves	243	32	124	3.87	3	15	P		

62.	56	Rectum	1	+	H	NS		Normal	201	36	114	3.16	3	15		+	
63.	61	Liver	–	+	H	Early LVH		Early LVH; loss of septal Q	329	—	—	——	3	15	P		
64.	64	Pancreas	1	+	V	NS		Normal	222	—	—	——	–	—			
65.	61	Stomach	–	+	—	LBBB		LBBB	640	56	421	7.51	3	26	P		
66.	60	Meninges	1	+	V	NS	+	Abnormal T waves; intermittent RBBB	372	45	215	4.77	3	14	P		
67.	35	Rectum	1	+	—	NS	+	LBBB and septal infarct	462	—	—	——	3	12			
68.	60	Stomach	1	+	V	NS	+	Abnormal T waves	262	—	—	——	9	13	P		
69.	61	? (General)	1	+	—	NS		Abnormal T waves; loss of septal Q	402	48	208	4.36	5	18			
70.	—	Esophagus	Trans.	+	—	Possible LVH; possible diaphragmatic infarct		Normal	—	—	—	——	3	13			
71.	63	Prostate	1	+	H	NS	+	Abnormal T waves	269	34	156	4.58	3	12		+	
72.	—	Ilium	1	+	—	NS		Emphysema; abnormal T waves	207	—	—	——	3	10			
73.	59	Larynx	1	+	V	Possible posterobasal scar	+	Agnormal T waves	380	48	232	4.83	3	9	P		
87.	61	Liver	1	+	—	NS		Low QRS; abnormal T waves	215	32	116	3.62	4	15			
88.	61	Liver	–	+	—	Posterobasal scar; LVH		LVH; high lateral scar	280	—	—	——	4	12			
89.	67	Stomach	1	+	V	Possible posterolateral scar		Abnormal T waves; emphysema	258	—	—	——	3	11			
74.	60	Kidney	1	+	V	NS	+	Abnormal T waves	445	46	237	5.16	3	11	P		
75.	62	Liver	–	+	—	Posterolateral infarct		Posterolateral infarct	280	48	145	3.02	3	13			
76.	58	Rectum	–	+	—	Anteroseptal infarct		Anteroseptal infarct	200	29	114	3.93	5	16	P		
77.	40	Rectum	1	+	V	NS		WPW; (? LVH)	438	57	250	4.38	5	20			
78.	56	Bladder	–	+	H	NS		Possible posterior infarct; Possible RVH	290	49	145	2.95	4	15	P		
79.	61	Stomach	1	+	V	Possible posterior infarct		Early LVH; loss of septal Q	388	57	199	3.50	4	15			
80.	56	Kidney	–	+	—	Possible posterior infarct		Loss of septal Q	393	70	205	2.92	3	18	P		
81.	81	Pancreas	–	+	—	NS		Abnormal T waves	252	30	117	3.90	3	12	P		
82.	64	Thyroid	1	+	—	NS		Loss of septal Q	150	20	83	4.14	3	13	P	+	
83.	65	Colon	–	+	—	Posterior infarct		Posterolateral infarct	313	33	160	4.84	3	15	P		
84.	66	Bladder	1	+	—	NS		Possible posterolateral infarct	433	46	235	5.12	3	19	P		
85.	57	Esophagus	–	+	—	Possible posterior infarct; RBBB		Possible posterior infarct and RBBB	220	—	—	——	4	—			
86.	59	Esophagus	–	+	—	NS		Abnormal T waves	236	26	114	4.38	3	13			

*Numbers 39-73 and 87-89 are cases without infarction. Numbers 74-86 are cases with infarction.

cardiogram showed changes considered typical of right ventricular hypertrophy in 4 patients (Patients No. 7, 13, 49, and 55). This finding was substantiated on postmortem examination in six of these eight (Patients No. 6, 13, 23, 27, 49, and 55), whereas the other two were just below the arbitrary limits of right ventricular hypertrophy. However, the right ventricles in these two were relatively large in comparison to the left ventricles. For example, in Patient No. 7 the right ventricle weighed 33 grams and the left ventricle weighed only 96 grams. In Patient No. 78 the right ventricle weighed 49 grams, whereas the left ventricle weighed 145 grams. (As noted later, most of these patients who died of malignant neoplastic disease, following a prolonged illness and marked cachexia, had small hearts.)

TABLE III. ACCURACY OF DIAGNOSIS OF HYPERTROPHY IN PRESENCE OF MALIGNANT NEOPLASIA

	ECG			SVCG		
	SUSPECTED*	CONFIRMED**	OVERLOOKED	SUSPECTED	CONFIRMED	OVERLOOKED
RVH						
Bronchogenic (38)	9	3	4	4	1	6
Nonbronchogenic (51)	5	2	4	4	2	4
LVH						
Bronchogenic	3	2	2	3	1	3
Nonbronchogenic	9	6	9	7	5	11

*Including appropriate bundle branch block and, for RVH, "emphysema patterns."
**Patient No. 67 with total heart weight of 462 grams is considered to have LVH.

Electrocardiographic evidence of left ventricular hypertrophy was considered to be present in 7 patients (Patients No. 20, 21, 57, 63, 77, 79, and 88). Spatial vectorcardiographic evidence of left ventricular hypertrophy[5] was present in 4 patients (Patients No. 20, 52, 63, and 88). There were findings of hypertrophy at autopsy in four of the seven with electrocardiographic evidence of left ventricular hypertrophy, and borderline in the other two (Patients No. 20 and 77). In the four patients with spatial vectorcardiographic evidence of left ventricular hypertrophy, the findings were evidence of left ventricular hypertrophy in one patient, borderline evidence in two, and absence of evidence in one (Table III).

Considering the presence of either the criterion of thickness or that of weight as necropsy evidence of hypertrophy in the right ventricle, this postmortem diagnosis was made in a total of 17 patients. The manifestations of right ventricular hypertrophy were present in the electrocardiograms in only six of these patients, and were evident in the spatial vectorcardiograms of three patients.

Similarly considering the criteria of either the thickness or the weight of the left ventricle as evidence of hypertrophy of that ventricle, LVH was present in 20 patients. Electrocardiographic evidence of left ventricular hypertrophy was present in only four of these patients, and hypertrophy was evident in the spatial vectorcardiogram of one patient.

The spatial vectorcardiograms were similar to normal Type 1 in 57 of the 89 patients. The P, QRS, and TsÊ loops of patients with bronchogenic carcinoma as a group were more vertically oriented and narrower in configuration than those of patients with malignant neoplasm of nonpulmonary origin (Figs. 1 and 3).

Distortion (Fig. 1,*b*), a manifestation of the QRSsÊ loop associated with aging, was present in 86 of the spatial vectorcardiograms, equivocal in three, and absent in only one in this entire series.

Examination of the coronary arteries revealed a high incidence of grossly prominent atherosclerosis, i.e., in 51 of 89 patients. Sixteen patients of this group had apparently normal electrocardiograms, including two patients (Patients No. 37 and 38) with myocardial infarctions demonstrated at autopsy.

Fifty-five of the 89 hearts weighed less than the frequently cited, arbitrary lower limit of normal weight of 275 grams.[3] The weight was 200 grams or less in 12 hearts. Metastatic lesions of the heart were found in seven of the patients with bronchogenic carcinoma and in three patients with malignant neoplasms which originated from other sites. In one patient (Patient No. 20) a lateral wall scar was suggested by both the electrocardiogram and the spatial vectorcardiogram, and was proved at autopsy to be a metastatic lesion in the lateral, or free, wall of the left ventricle.

DISCUSSION

The QRSsÊ loop was vertically oriented in 25 of the 38 patients with bronchogenic carcinoma. There was a striking similarity of form between the narrow QRSsÊ loops of this group of patients and those of the normal Type 1 previously described for young healthy males.[2] In contrast, the vertical orientation of the QRSsÊ loop was present in only 22 of the 51 patients with the nonbronchogenic carcinomata; the majority of the patients had loops of a much more open configuration (Fig. 1,*b*). The significance of this difference is speculative, but it is suggested that the vertical position of the sVCG may have been acquired. If so, such orientation may thus be an early indication of secondary pulmonary circulatory changes associated with bronchogenic carcinoma, as well as possibly associated with the cachexia of malignancy. A possible alternate mechanism such as vertical position resulting from the lowered diaphragm in emphysema cannot, of course, be excluded. Although the groups were small and the absolute weights not strikingly abnormal, there appeared to be a real difference in the relative size of the right and left ventricles between the bronchogenic and nonbronchogenic groups (see Fig. 4). Thus, the vertical orientation of the QRSsÊ loop may indirectly reflect the myocardial response as to which of the major segments of the circulation contains the carcinoma.

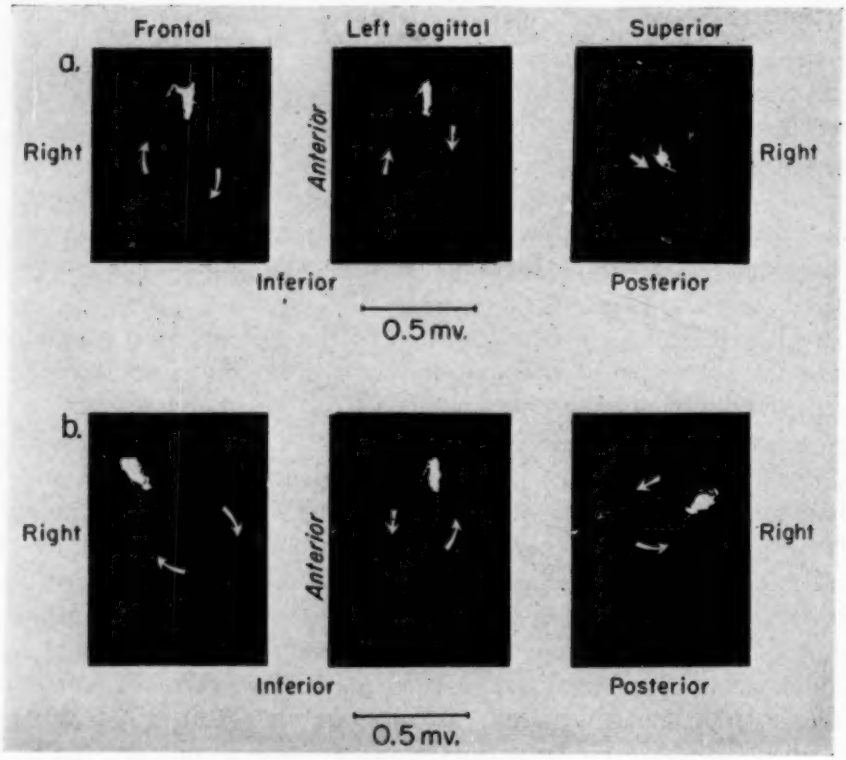

Fig. 1.—Spatial vectorcardiograms of subjects with carcinoma of the stomach (Patients No. 39 and 56). Note the thin, vertically oriented QRSsÊ loop in *a* and the more open, semivertical, but distorted QRSsÊ loop in *b*.

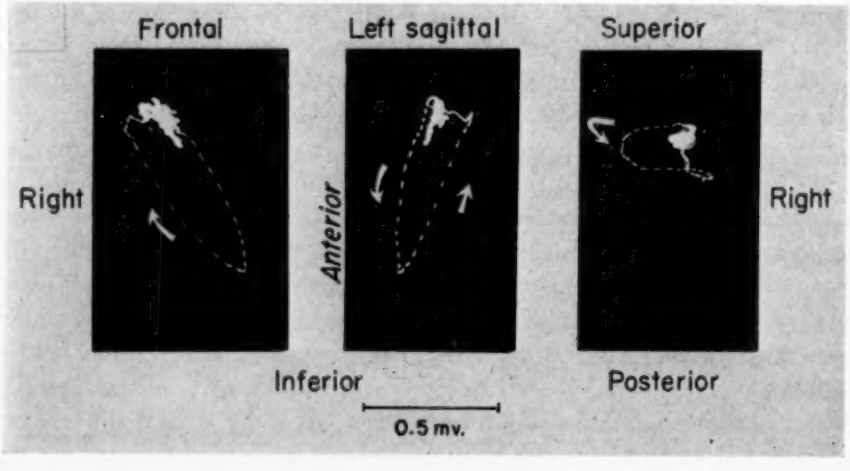

Fig. 2.—Spatial vectorcardiogram of a subject with bronchogenic carcinoma (Patient No. 1). Note the vertical orientation and terminal slowing. See text for discussion.

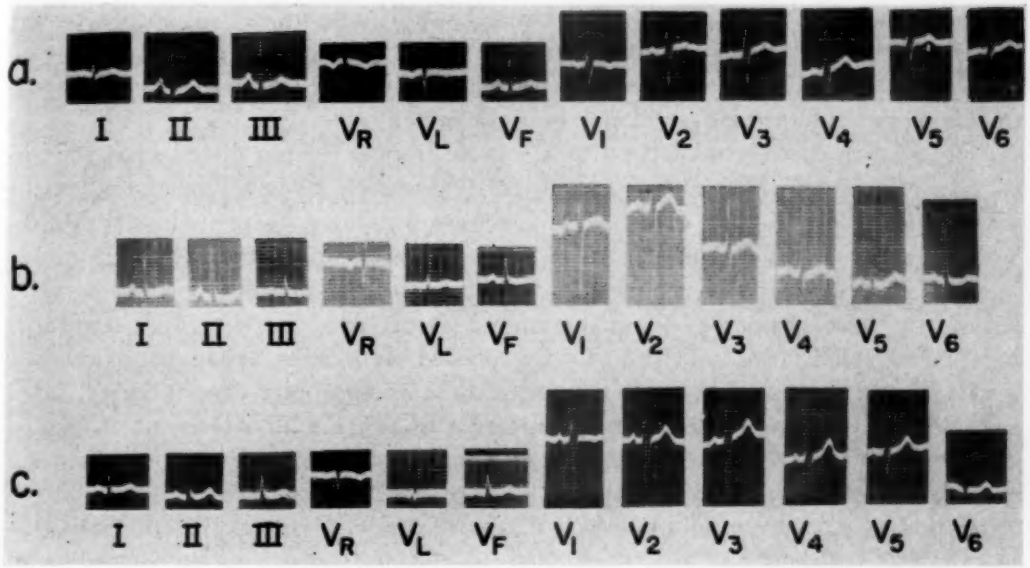

Fig. 3.—Electrocardiograms of patients with carcinoma. These tracings were recorded at the same time as the spatial vectorcardiograms shown in Figs. 1 and 2; *a* is from Patient No. 39; *b* is from Patient No. 56; *c* is from Patient No. 1.

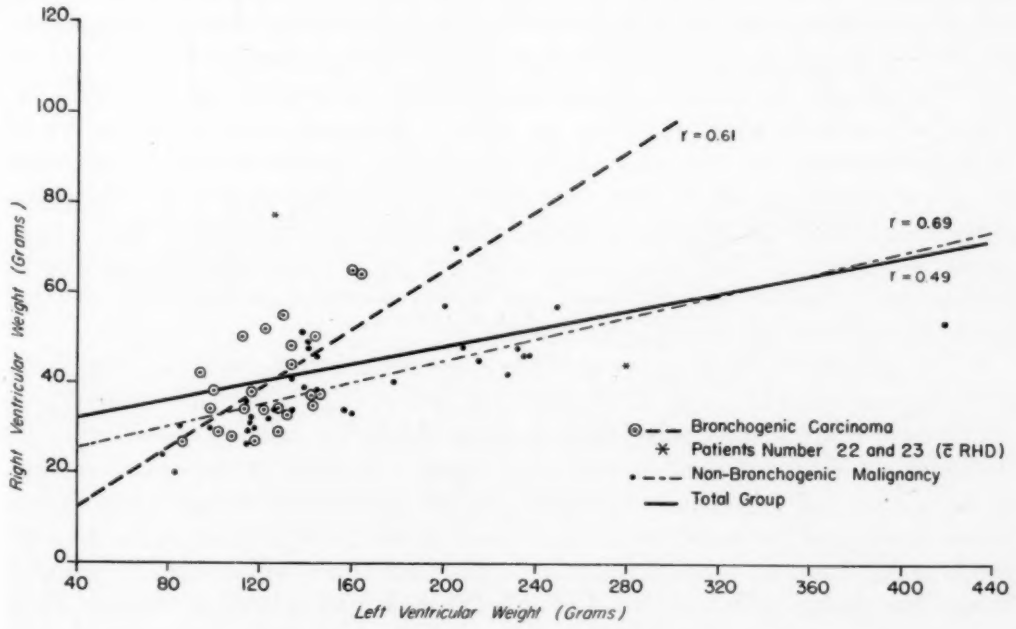

Fig. 4.—Relationship between right and left ventricular mass of 61 hearts from patients with malignant neoplasia. Note the steeper slope of the line of regression of the bronchogenic group compared with that of the nonbronchogenic group. See text for discussion.

The incidence of distortion exceeded the anticipated occurrence of this characteristic in the QRSsÊ loop of clinically normal people.[5] Whether or not this finding indicates accelerated aging in these patients and in their hearts, or is a manifestation of wasting of cardiac muscle and associated damage due to the malignant process could not be determined.

Reduction in weight of the heart muscle frequently paralleled that seen in the gross body weight. Brown, small cardiac muscle relatively denuded of fat with resulting prominence of the surface vessels was often quite striking. Microscopically there was fragmentation of muscle fibers, prominence of their nuclei, increase in lipochrome pigment, and diminution of fat content in the hearts of several of these patients. When carcinoma is present, the accepted standards for distinguishing normal from hypertrophied ventricles apparently are not applicable. It seems reasonable to suggest that hypertrophy cannot be excluded pathologically when borderline measurements of ventricular weight or thickness are present in a heart that reflects the emaciation of cancer. Furthermore, when the electrocardiogram and spatial vectorcardiogram are compared with the autopsy findings in a patient who is rapidly losing weight and deteriorating in health, there should not be a long interval of time separating the recording of the electrical activity of the heart and the autopsy findings. Evidence of ventricular hypertrophy was obtained at autopsy in several patients without ECG or sVCG manifestations of hypertrophy. It is understandable that the electrocardiographic and spatial vectorcardiographic configurations of hypertrophy could be masked by associated disturbances in conduction, bilateral ventricular hypertrophy, or myocardial infarction, but in several instances without these functional and anatomic changes there was no recognizable electrocardiographic or vectorcardiographic manifestations of ventricular hypertrophy.

The presence of malignant neoplasm is characterized by wasting and starvation of the entire body, including the heart. This unique organ also responded to the stimulating stresses, such as that due to high resistance in the pulmonary circuit produced by the chronic pulmonary disease associated with carcinoma of the lung. It would appear significant, therefore, that right ventricular hypertrophy was present in 17 hearts (and left ventricular hypertrophy in 20 hearts) despite the cachectic, malnutritional, and toxic state associated with a prolonged illness due to malignant neoplastic disease.

The almost total loss of fat and the decrease in cellular mass is compatible with the concept that with starvation and diseases in cancer the patient uses all possible sources of energy, even parts of the living cells. As evidenced by the marked microcardia and associated changes, this included the hearts of many of the patients of this series. However, a most interesting biologic phenomenon noted in some of the patients was the result of the conflict between the biologic forces which tend to make a ventricle small and those which tend to make it large. For example, Patient No. 1 (Table I; Fig. 2) had pulmonary disease which apparently produced pulmonary hypertension and, in turn, stimulated right ventricular hypertrophy. Simultaneously, the chronic debilitating influence of the malignancy tended to reduce the size of the ventricles. In this patient the pulmonary hypertension was the greater of the two forces. Right ventricular

hypertrophy developed and remained—or, at least, the right ventricle did not contribute proportionately or in large quantity its muscle mass as a source of energy to meet the needs of the body during the final weeks of the patient's life. However, the adjacent left ventricle, without a heavy work load, or even a lessening work load, contributed relatively more of its precious myocardial cellular mass to the energy pool to keep the organism alive as long as possible. The two opposing forces, one stimulating hypertrophy and the other atrophy, may thus act simultaneously with different magnitudes of effect upon the two ventricles of the same heart. A study of Table I reveals several other such instances. This antagonism of two fundamental biologic phenomena in man is of considerable interest and needs study.

SUMMARY

This paper is a correlative study of the electrocardiogram and spatial vectorcardiogram with the heart at autopsy in 89 patients with carcinoma. Analysis of the QRSsÊ loops revealed an increased frequency of narrowed Type-1 loops in the patients with bronchogenic carcinoma. Distortion of the QRSsÊ loop, such as reported previously for normal aging people, was present in nearly every patient in this series. There was a significant number of patients who demonstrated pathologic evidence of right or left ventricular hypertrophy, but in whom the ventricular hypertrophy was not definitely recognizable from the electrocardiogram or the spatial vectorcardiogram.

A number of patients showed a greater influence upon the heart of the stimulus for ventricular hypertrophy, than the stimulus for ventricular atrophy associated with the extreme cachexia of prolonged illness with ultimate death from carcinoma, when both stimuli were existent simultaneously.

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An Electrocardiographic and Spatial Vectorcardiographic Pattern Associated With Diffuse Myocardial Damage and Ventricular Aneurysm

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During a recent study of the relationship between the spatial vectorcardiogram and the pathologic manifestations in myocardial infarction, a vectorcardiographic and electrocardiographic pattern associated with widespread myocardial scarring and aneurysmal bulging of one or more portions of the left ventricular cone was noted.[1] This report concerns a study of such patterns which apparently reliably indicate widespread damage to the myocardium.[4] Although this spatial vectorcardiographic (sVCG) pattern was described previously, it was not correlated with necropsy data.

METHODS AND MATERIALS

From a series of vectorcardiograms recorded over a period of 30 months at the New Orleans Veterans Administration Hospital, autopsies were obtained in 160 patients, 59 of whom were found to have myocardial scarring or infarction. Both the hearts and the electrocardiograms of these and 525 other patients who died during the same period were examined for pathologic evidence of ventricular damage or aneurysm and the presence of the distinctive pattern. Instances either of complete transmural scarring with thinning and bulging of the heart wall or of abrupt localized change in the radius of mural curvature were considered to be aneurysms. A total of 24 patients having myocardial infarction and scarring with ventricular aneurysms (Group A) were thus available for study. Four patients were found to have myocardial infarction without ventricular aneurysm but with the characteristic electrocardiographic pattern to be described (Group B). The electrocardiograms were recorded by conventional methods with a string galvanometer; spatial vectorcardiograms were recorded as previously described, using the equilateral tetrahedron as the reference system.[2]

RESULTS

Clinical Findings.—All 24 patients with ventricular aneurysms had symptomatic heart disease: 23 had one or more episodes of myocardial infarction and 14 had angina pectoris, while the remaining patient (Patient No. 23, Fig. 1) had

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congestive heart failure without history of chest pain. In Group B, 3 of the 4 patients had symptomatic heart disease, and the other (Patient No. 27, Fig. 1) died in renal failure following surgery for arteriosclerotic gangrene of the foot.

Anatomic Findings.—Both groups of patients had hearts with widespread, extensive myocardial scarring and infarction. In 14 (including that of Patient No. 28 from Group B) of the 20 ventricles mapped in detail (Fig. 1), all four quadrants of the left ventricular cone had infarction or scar ring; 4 hearts had three quadrants involved; and in 2 hearts only two quadrants were infarcted. The apex was extensively damaged in all patients except one (Patient No. 23, Fig. 1). In only one patient (Patient No. 24, Fig. 1) was there neither occlusion nor severe narrowing of the left anterior descending coronary artery.

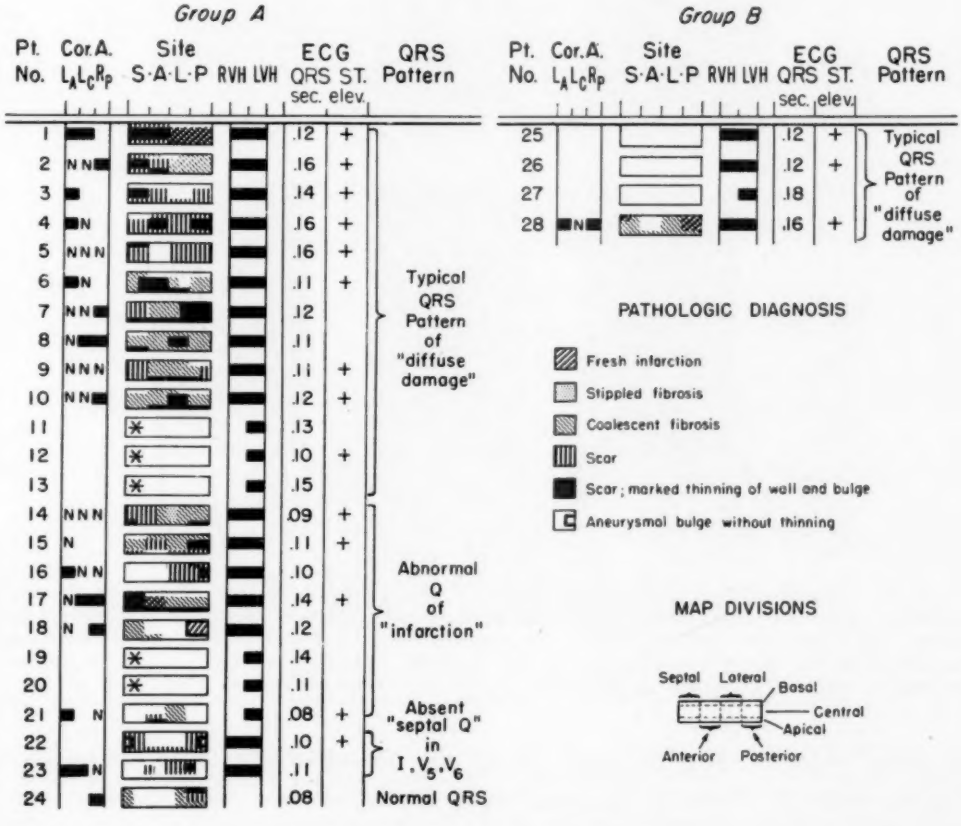

Fig. 1.—Summary of the major clinical, anatomic, spatial vectorcardiographic, and electrocardiographic findings in 24 patients with cardiac damage and left ventricular aneurysm, and in 4 other patients without ventricular aneurysms but with the ECG pattern characteristic of diffuse myocardial damage.

In 17 hearts the formation of the aneurysm was the result of marked thinning of a solid transmural scar, and in 2 hearts there was aneurysmal bulging of the ventricular wall at sites which were nearly normal in thickness and composed predominantly of muscle, with scattered scarring being noted on histologic examination (Patients No. 18 and 22, Fig. 1). The aneurysms were located most frequently on the diaphragmatic, anteroseptal, and apical portions of

the left ventricular cone. There was no definite relationship between the location of the arterial occlusion and the site of aneurysmal formation. Most aneurysms were single, but in each of 3 hearts there were two small aneurysms (Patients No. 2, 4, and 8, Fig. 1).

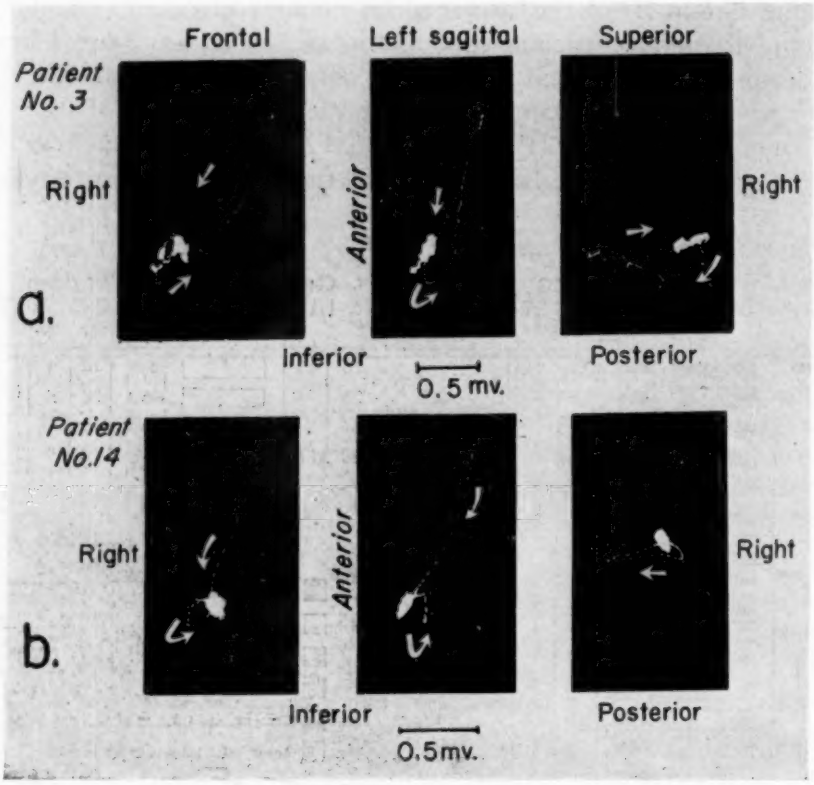

Fig. 2.—Spatial vectorcardiograms of 2 patients with diffuse myocardial damage and ventricular aneurysm. In *a*, the accompanying electrocardiogram had the characteristic pattern simulating left bundle branch block described in the text (see Fig. 4,*a*); but in *b*, the accompanying electrocardiogram was that of lateral myocardial infarction without conduction defect (see Fig. 4,*b*). Note the slowing and wavy irregularity of contour of the QRSsÊ loop in *a* as compared to that in *b*.

The Electrocardiogram and Spatial Vectorcardiogram.—The electrocardiographic pattern consisted of a prolonged QRS complex (0.10 to 0.16 second in duration), predominantly upright in Leads I, V_5, and V_6—but differing from classic left bundle branch block in that there was a brief initial upward deflection followed by a shallow, downward deflection and then a prominent prolonged R′ in one or more of these three leads. The accompanying sVCG displayed a slurred, narrow, distorted QRSsÊ loop oriented mainly upward and slightly posteriorly and to the left but always partly to the right of the isopotential point when viewed in the frontal plane projection (Fig. 2). The direction of rotation of the trace was not uniform (Figs. 2 and 3), but in all instances the tracings suggested infarction of the lateral wall of the left ventricle by either an arc-like deformity with concavity directed to the right or a rapid straight up-

stroke.[1,3] The early rightward displacement of the QRSsÊ loop (corresponding to the early downward deflection in Leads I, V_5, or V_6) suggested either septal infarction in the presence of left bundle branch block or infarction of the lateral wall of the left ventricle with associated disturbances in the order and rate of spread of the process of depolarization. A remarkably similar sVCG was seen in 7 of 11 patients with ventricular aneurysm (Patients No. 1-7), including 2 patients who did not have the electrocardiographic pattern described above and 1 patient without a ventricular aneurysm.

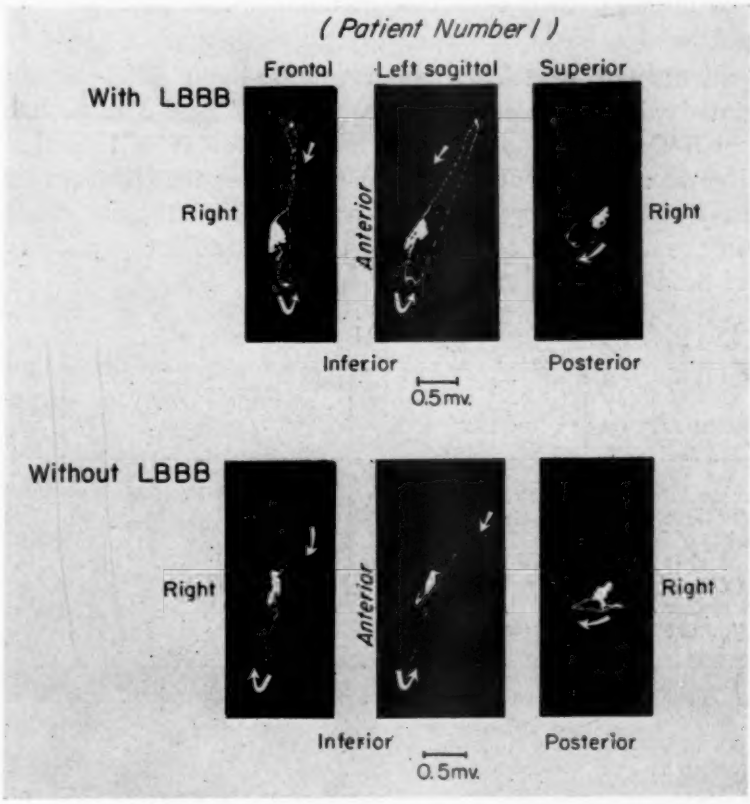

Fig. 3.—Spatial vectorcardiogram of a patient with diffuse myocardial damage and ventricular aneurysm and intermittent left bundle branch block. The upper views are of a ventricular beat with classic LBBB, and the lower views are of a "normally" conducted beat. Note the similarity in configuration between the beat with conventional LBBB and the beat without, except for the early portion of the QRSsÊ loop directed to the right of the isoelectric point in the latter (see Fig. 4,*c*).

The electrocardiogram and the spatial vectorcardiograms of a patient with intermittent left bundle branch block (Patient No. 1, Fig. 1) had both the pattern associated with ventricular aneurysm and diffuse myocardial disease as well as that associated with LBBB (Fig. 3). This patient's sVCG had a rapid vertical upstroke (suggesting infarction of the lateral wall) and the small downwardly concave arc (suggesting infarction of the diaphragmatic wall) in the QRSsÊ loop when the pattern was present or absent.

The electrocardiographic pattern described above was found in 13 of the 24 patients with ventricular aneurysm (Table I). Eight of the 13 patients had a persistent elevation of the S-T segment. Eight of the 11 remaining patients had tracings diagnostic of infarction by conventional criteria, and 4 of these 8 had persistent elevation of the S-T segment. In 2 patients the only abnormality other than persistent elevation of the S-T segments was the absence of Q in Leads I, V_5, and V_6 (Patients No. 22 and 23, Fig. 1). In one of these 2 patients as well as in another (Patient No. 18, Fig. 1) the wall of the aneurysm was of muscle and not of thin scar tissue. Neither myocardial infarction nor ventricular aneurysm was suspected in one patient even though the T waves were abnormal (Patient No. 24, Fig. 1).

Of 24 patients with ventricular aneurysms, 13 had a QRS pattern considered to be associated with "diffuse myocardial damage," and 5 more had persistent shifting of the S-T segment, so that there was thus a total of 18 patients in whom it was possible to suspect ventricular aneurysm from the electrocardiogram. Of the 4 patients in whose tracings the QRS pattern of "diffuse myocardial damage" was found in the absence of aneurysm of the heart at autopsy, 3 had persistent elevations of the S-T segment.

TABLE I

ABNORMALITY OF QRS COMPLEX	NUMBER OF CASES	PERSISTENT S-T ELEVATION
With Ventricular Aneurysm	24	13
Typical "diffuse damage" pattern	13	8
Abnormal Q of infarction	8	4*
Absent septal Q in Leads I, V_5, V_6	2	1
Normal QRS	1	0
Without Ventricular Aneurysm		
Typical "diffuse damage" pattern	4	3

*This does not include 1 new elevation associated with fresh infarction.

DISCUSSION

The presence of an initial, though at times very small, upward deflection of the QRS complex in Leads I, V_5, and V_6 and the early downward deflection in these leads in association with a specific anatomic distribution of myocardial infarction differentiates this electrocardiographic pattern from classic left bundle branch block. The spatial vectorcardiograms strongly resembled those previously described in a study of LBBB, wherein the patients were suspected clinically of having diffuse myocardial damage.[4] An explanation as to the origin of such a configuration can only be speculative. In addition to functional disturbances in the conduction system, the QRS prolongation and deformity could result from alterations in the process of ventricular depolarization associated with infarction and the accumulation of scar tissue. For example, the early leftward spatial course of depolarization could be due to the loss of an initial normal rightward activation of the interventricular septum because of either

defects in conduction in the left bundle branch or disease or loss of muscle in the leftward septum. After the initial small migration the mean activation to the right beyond the expected time for the normal septal Q may be due to associated damage to the lateral wall. It was suggested previously that the wide Q in precordial leads recorded to the left of the transition zone in infarction of the lateral wall contained two components: the normal septal Q followed by an abnormal Q due to the infarction.[5] Chapman and Pearce[6] have recently described an "rsR" pattern" in Leads I, V_L, and V_6 as a sign of anteroseptal infarction, and have similarly considered the small relatively early "S" as a "delayed Q." Increase in duration of the QRS (wide R') may be further evidence of widespread damage to the myocardium. The autopsy findings show the pattern to be associated with myocardial disease and ventricular aneurysm. The number of patients studied is relatively small.

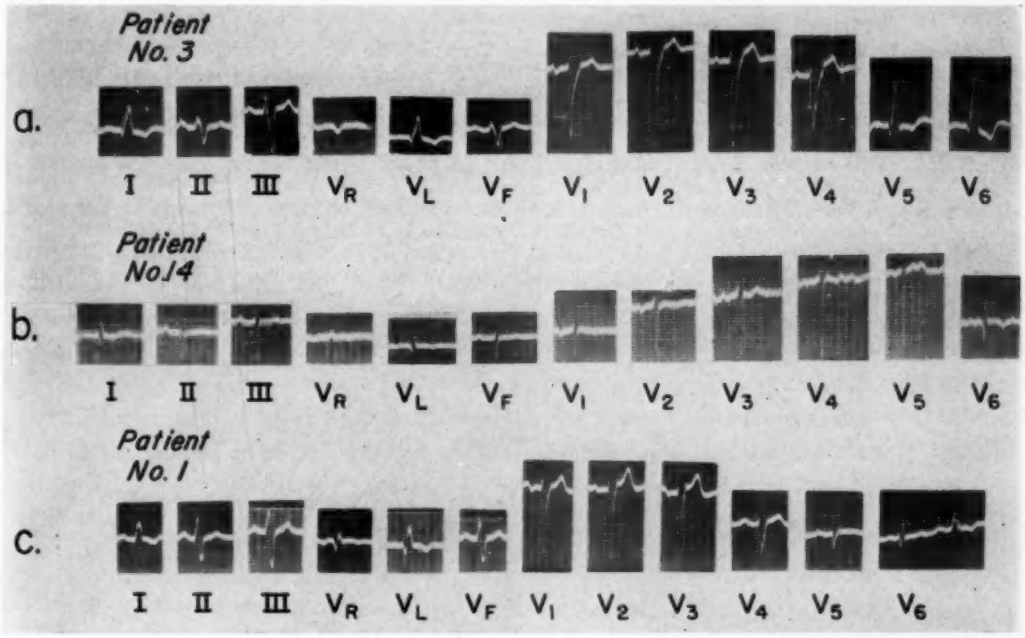
Patient No. 3
a.
I II III VR VL VF V1 V2 V3 V4 V5 V6
Patient No.14
b.
I II III VR VL VF V1 V2 V3 V4 V5 V6
Patient No. 1
c.
I II III VR VL VF V1 V2 V3 V4 V5 V6

Fig. 4.—Electrocardiograms from the patients whose spatial vectorcardiograms are shown in Figs. 2 and 3. For Patient No. 1 note the early downward deflection in the first ventricular beat in Lead V_6, which is not seen in the second beat of LBBB in that lead.

Until the order of ventricular depolarization in health and in disease for man is known, any explanation for the sVCG and ECG described is guesswork. Although these patterns are not pathognomonic of diffuse myocardial damage, they were found uniformly in association with autopsy evidence of diffuse myocardial damage. Because persistent elevation of the S-T segment was found in the tracings of 3 patients with infarction but without associated aneurysm, as well as in those of patients with aneurysm, the mechanism for the deviation of the S-T segment from the isoelectric line in severe diffuse chronic myocardial disease with infarction remains to be explained satisfactorily.

SUMMARY

Aspects of clinical, pathologic, electrocardiographic, and spatial vectorcardiographic findings in 24 patients with diffuse myocardial damage, infarction, and ventricular aneurysm have been described. A distinctive QRS pattern (0.10 to 0.16 second) in Leads I, V_5, or V_6 characterized by a brief early upward deflection followed by a shallow downward deflection and, finally, a prolonged prominent R′ was found in 13 patients. Persistent elevation of the S-T segment was noted in 5 of the remaining patients. The same QRS pattern was found in 4 other patients with myocardial infarction and diffuse scarring but without ventricular aneurysm.

We wish to thank Dr. Joseph Ziskind for his assistance and the use of his facilities in the Department of Pathology.

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Case Reports

Primary Tumor of the Heart: Report of a Case With Myxofibroma of the Right Ventricle

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Primary tumor of the heart is rare, and worth reporting. Lymburner[1] collected 226 cases of primary tumors of the heart from the literature up to 1934. In 1951, Prichard[2] collected 447 reported cases and added four cases of his own.

Among primary tumors of the heart, myxoma is the most common, and about 200 cases of myxoma have been reported. Ranking next to myxoma are sarcoma, rhabdomyoma, and fibroma, all common, and ranking in frequency in the order given. Recently, we had an opportunity of observing a case of myxofibroma of the right ventricle, diagnosed at autopsy. The patient had had several episodes of syncope and died during the last of these episodes. This case will be presented in detail in this paper because of its apparent rarity and because of the location of the tumor.

CASE REPORT

M.N., a 27-year-old Japanese housewife, was admitted to the hospital on Jan. 28, 1958, with a history of several episodes of syncope followed by convulsive movements of the extremities. Her family history was noncontributory. At age 10 she had suffered from diphtheria, but recovered completely without any complications. She had never been suspected of having any congenital or acquired heart disease prior to admission. She had her first delivery on Oct. 17, 1957, at age 26. In December, two months postpartum, she began to experience easy fatigability and palpitation on exertion. On Jan. 11, 1958, when she was in a closed room with her friends, an attack of syncope occurred suddenly, lasting a few minutes, and was followed by a tonic convulsion of the extremities. The patient was unconscious and cyanotic during the attack. Her face was pale and the pulse was very faint and weak. After recovery from the attack she complained of shortness of breath. On Jan. 27, 1958, a similar attack occurred, lasting five minutes, and also followed by a convulsion. On the next day, January 28, she had a third attack of syncope and was admitted to the hospital.

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Physical Examination.—On admission, examination revealed a well-developed and well-nourished woman. The sensorium was clear. She appeared somewhat anxious. Cyanosis was present in the lips and cheeks. Respiration was rather shallow at 25 per minute. Pulse was 100 per minute, regular, weak and faint. Blood pressure was 80/60 mm. Hg in the right arm. Temperature was normal. Tonsils were normal and there was no lymphadenopathy. The heart was enlarged on percussion one fingerbreadth to the left of the mid-clavicular line. The apical impulse was in the fifth intercostal space just outside the mid-clavicular line. There was a Grade 4 systolic murmur in the second intercostal space at the left sternal border. The second sound in the pulmonary area was weak, but audible. There was no thrill. Slight venous distention was found in the neck. The lungs were clear. The liver was palpable one and one-half fingerbreadths below the right costal margin at the right mid-clavicular line. Neither spleen nor kidneys were palpable. There was no edema of the legs.

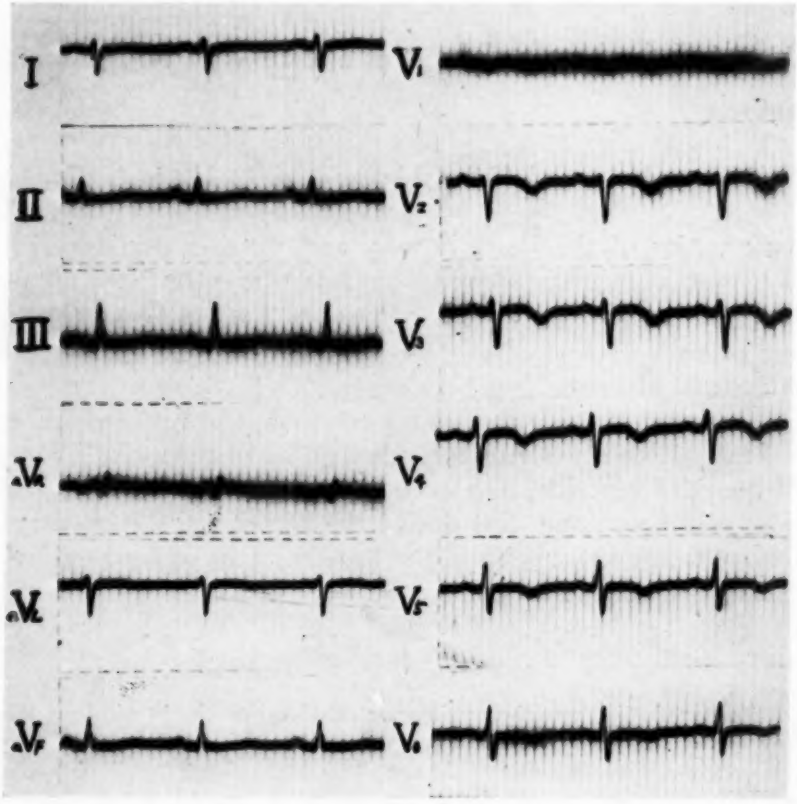

Fig. 1.—Electrocardiogram taken on admission shows sinus rhythm, right axis deviation, negative T waves in Leads V_1-V_6. The QRS complexes in Leads V_1-V_4 show rs or rS patterns.

An electrocardiogram showed sinus rhythm, right axis deviation, and negative T waves in all the chest leads. The QRS complexes in Leads V_1-V_4 showed rS or rs patterns (Fig. 1).

Chest x-ray studies (Fig. 2), including fluoroscopic examination, revealed convexity of the pulmonary artery salient, but an exaggerated pulsation of the corresponding area was not seen. The lung markings were diminished.

Laboratory Examination.—Hemoglobin content of the blood was 13.5 Gm. per 100 ml. Red blood cell count was 4.29 million, with a hematocrit of 43 per cent. White blood cell count was 7,800, and no abnormality was found on differential count. Platelet count was 160,000 by Fonio's

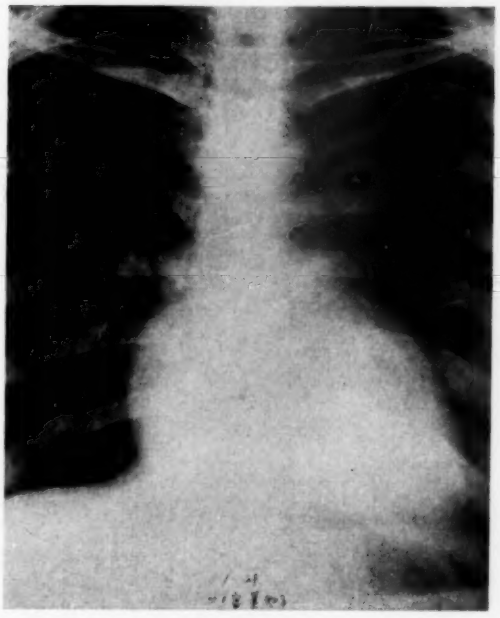

Fig. 2.—X-ray film of the chest.

Fig. 3.—Macroscopic findings at autopsy. Polypoid tumors of various shapes and sizes in the right ventricle and the pulmonary artery.

method. Erythrocyte sedimentation rate was 1.5 mm. in one hour. Serum protein was 5.1 Gm. per 100 ml. Electrophoretic studies of serum showed a decrease in the albumin fraction and an increase in the globulin fraction. Potassium content of the serum was 7.8 mEq./L.; sodium content was 141.5 mEq./L.; and calcium content was 4.9 mEq./L. Nonprotein nitrogen level of the serum was 36 mg. per 100 ml. Blood Wassermann was negative.

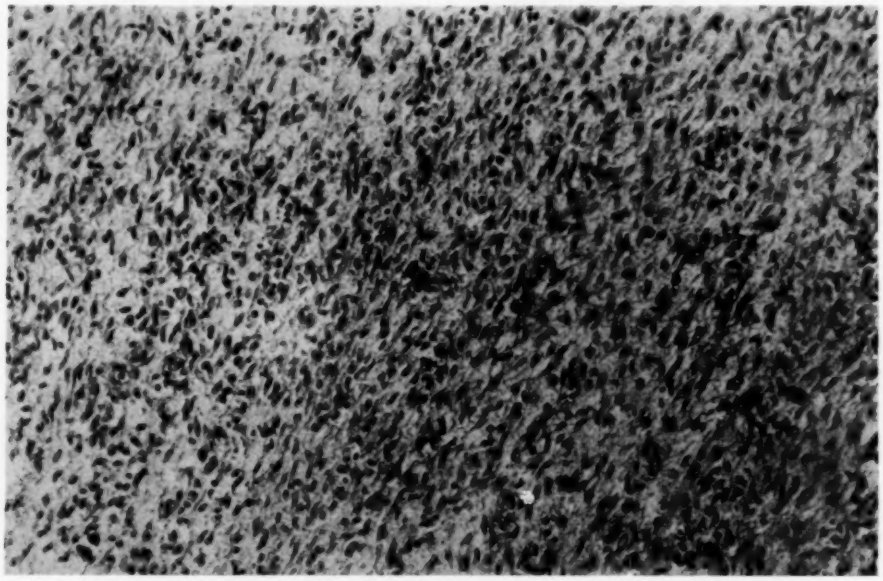

Fig. 4.—Microscopic finding at autopsy. There were abundant fibers and spindle cells, and poor stroma (hematoxylin and eosin; ×100).

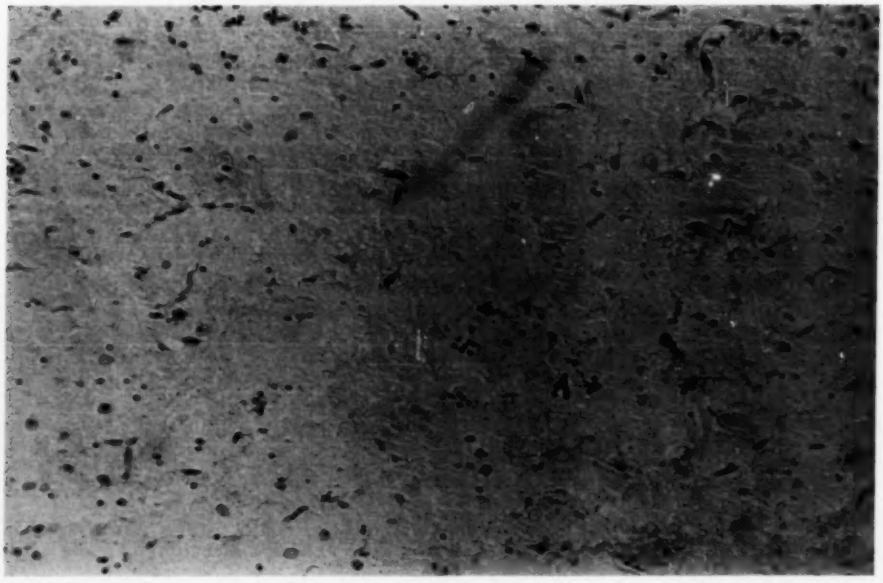

Fig. 5.—Microscopic finding at autopsy. There were a few fibers and spindle cells, and abundant stroma (hematoxylin and eosin; ×100).

Clinical Course.—A small dose of digitalis was given orally, and plasma infusions were given to correct the dysproteinemia. Nevertheless, spontaneous attacks of syncope occurred on January 29, February 2, 14, and 29, and the patient died on February 29, 1958, during an attack.

Autopsy Findings.—The heart weighed 399 grams. The right ventricle was greatly dilated and hypertrophied. Surprisingly, seventeen polypoid tumors were observed in the right ventricular chamber and the lumen of the pulmonary artery, arising from the endocardium of the right ventricle and the intima of the pulmonary artery (Fig. 3). The tumors were yellowish gray in appearance and soft. Tumors were found in the pocket of the pulmonary cusp. The largest tumor was in the right ventricle, arising from the endocardium near the pulmonary valve on a relatively long and easily movable stalk.

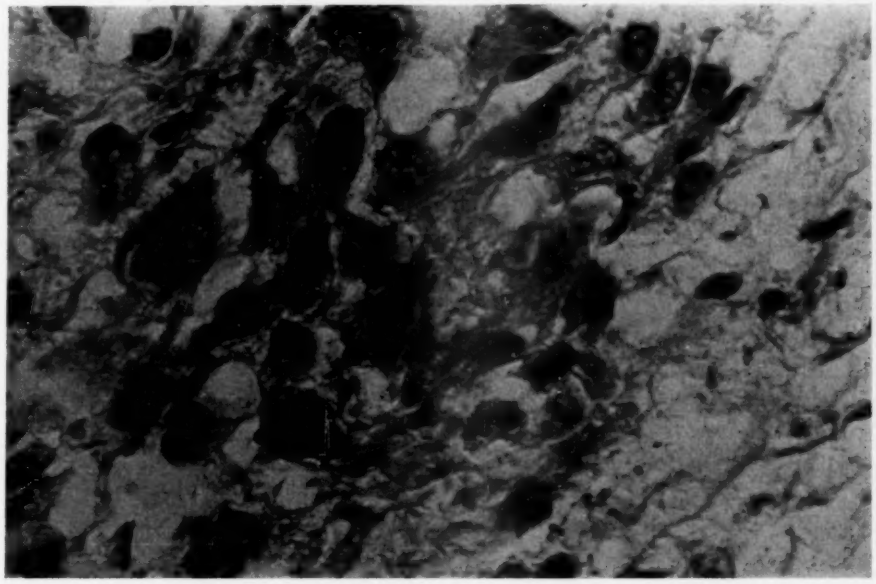

Fig. 6.—Microscopic finding at autopsy. Mitoses were seen rather frequently (hematoxylin and eosin; ×400).

A diagnosis of myxofibroma was made histologically. Microscopically, abundant fibers and spindle cells with poor stroma were found in the sectioned preparations from most of the tumors, suggesting fibroma (Fig. 4). In some tumors, however, there were several areas consisting of a few fibers and spindle cells with abundant homogeneous stroma, suggesting myxoma (Fig. 5). Although the morphologic patterns seemed to be benign, mitoses were seen rather frequently in some parts of the tumor (Fig. 6). The tumors were limited to the endocardium and did not infiltrate into the myocardium.

COMMENT

It has already been pointed out that change of position and infusion of fluid often results in a fainting attack in a patient who has an intracavitary polypoid tumor of the heart,[3] although the exact mechanism underlying the attack remains unknown. This patient had similar attacks several times in the course of her illness. In this case, however, it seems likely from the autopsy findings that the attacks of syncope observed were due to transient obstruction of the pulmonary ostium by tumor in the right ventricle. Death probably resulted from prolonged obstruction.

Pathologically, the nature of so-called myxoma of the heart still remains shrouded in mystery. Two different concepts have been presented. One is the non-neoplastic,[4,5] and the other the neoplastic theory.[2,6] According to the former, the so-called myxoma is interpreted as a large thrombotic mass. The myxoma is found most frequently in the left atrium, where it produces the syndrome of paroxysmal cyanosis, syncope, and the murmur of mitral stenosis. Myxoma is seldom encountered in the right ventricle or the pulmonary artery, although these are relatively common sites of fibroma and sarcoma.[2]

Making the diagnosis of a primary tumor of the heart is usually difficult. Clinically, angiocardiography is most helpful in the diagnosis of intracavitary cardiac tumors.[3,7] Successful removal of the tumors has been reported recently in increasing numbers,[8-12] but recurrence must be taken into consideration.

SUMMARY

A case of myxofibroma of the right ventricle observed in a twenty-seven-year old Japanese woman is described.

We wish to thank Professor Dr. K. Nakao and Professor Dr. M. Murakami for revision of this paper, and Professor Dr. G. Ohneda for providing the pathologic findings.

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Idioventricular Parasystole With Exit Block in a Subject With Complete Atrioventricular Dissociation

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Parasystole is a very rare disturbance of rhythm in which two or more centers concurrently and independently produce effective impulses, without disturbing the conduction of stimuli.

A parasystolic mechanism must be suspected in those cases of arrhythmia in which the unifocal ectopic systoles present a variable coupling and the length of intervals between two consecutive ectopic systoles stand in simple mathematical relation to one another, and some systoles, called "fusion systoles," present a morphology and an appearance which are closely related to the contemporary activity of both centers.

The ectopic center may be located either in the auricles or, as happens more frequently, in the ventricles, and has the capacity to interfere with the activity of the sinus node. There are two classic forms of parasystole: (1) *parasystole with simple interference*, in which the rate of impulse production of the ectopic center is lower than that of fundamental rhythm, and every ectopic impulse falling outside the refractory period becomes effective; and (2) *parasystole with exit block*, in which the rate of impulse production of the ectopic center is higher than that of fundamental rhythm, but not all impulses falling outside the refractory period become effective.

In all cases of both types reported to date, fundamental rhythm is governed by the sinus node, and the parasystolic center is located either in the auricles or, more frequently, in the ventricles.[2,6-9] The case we observed is an exceptional instance of atrioventricular dissociation and idioventricular parasystole.

CASE REPORT

The electrocardiographic recordings were made on an 8-year-old boy affected by diphtheric myocarditis accompanied by a severe toxic state which led to death during the eighth day of disease.

The first electrocardiogram, recorded on Lead III, shows dissociation due to complete atrioventricular block (Fig. 1). The auricles appear to be governed by the sinus node, whose impulses have a cycle length of 0.58 to 0.78 second. The ventricles produce impulses at a very much lower

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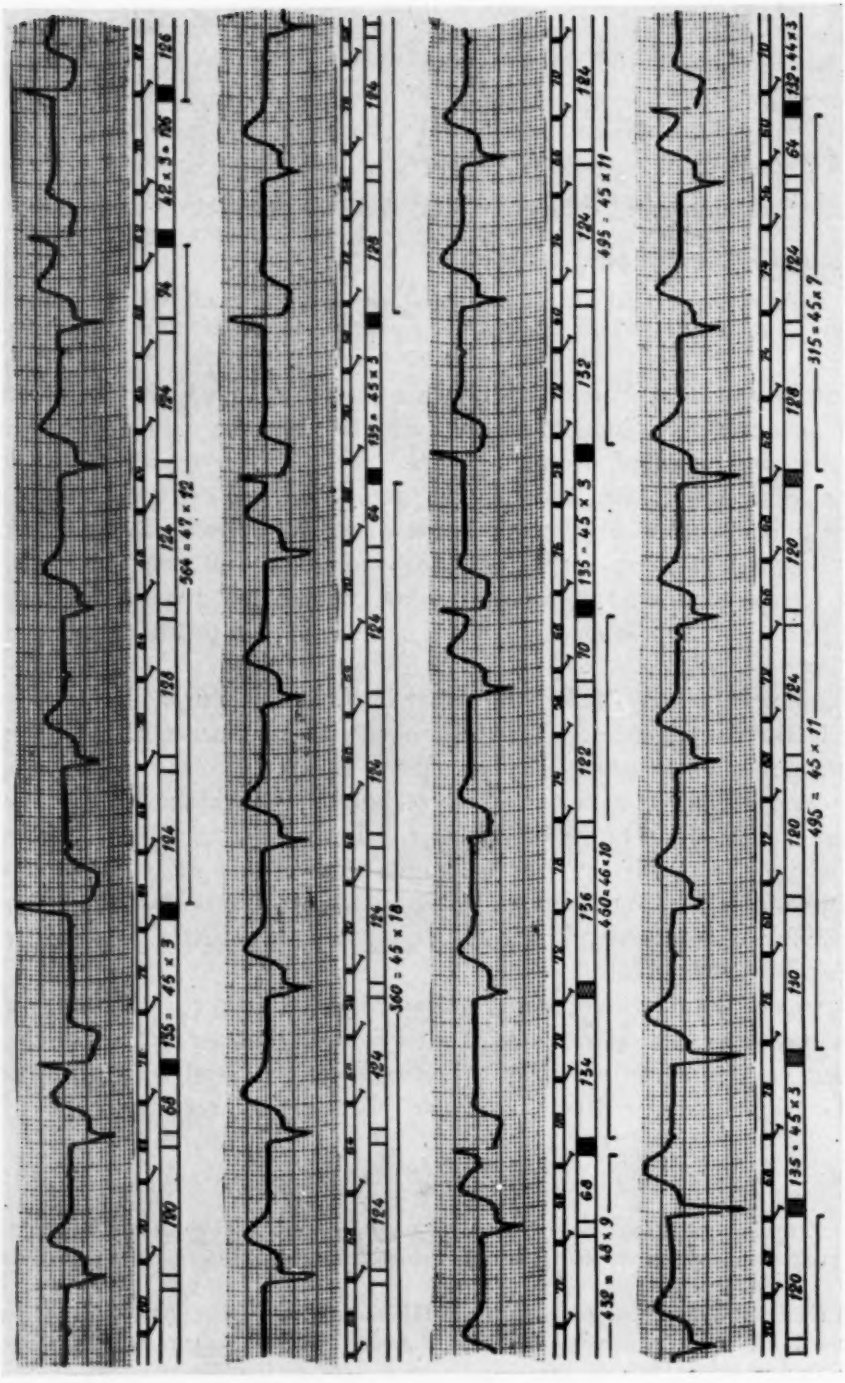

Fig. 1.—Electrocardiogram recorded in Lead D_3. In the first line of the markings the black rectangles show the blocked atrial beats. In the third line the white squares show the beats of the first ventricular paracenter, the black squares show the beats of the second ventricular paracenter, and the discontinuous squares show the fusion beats.

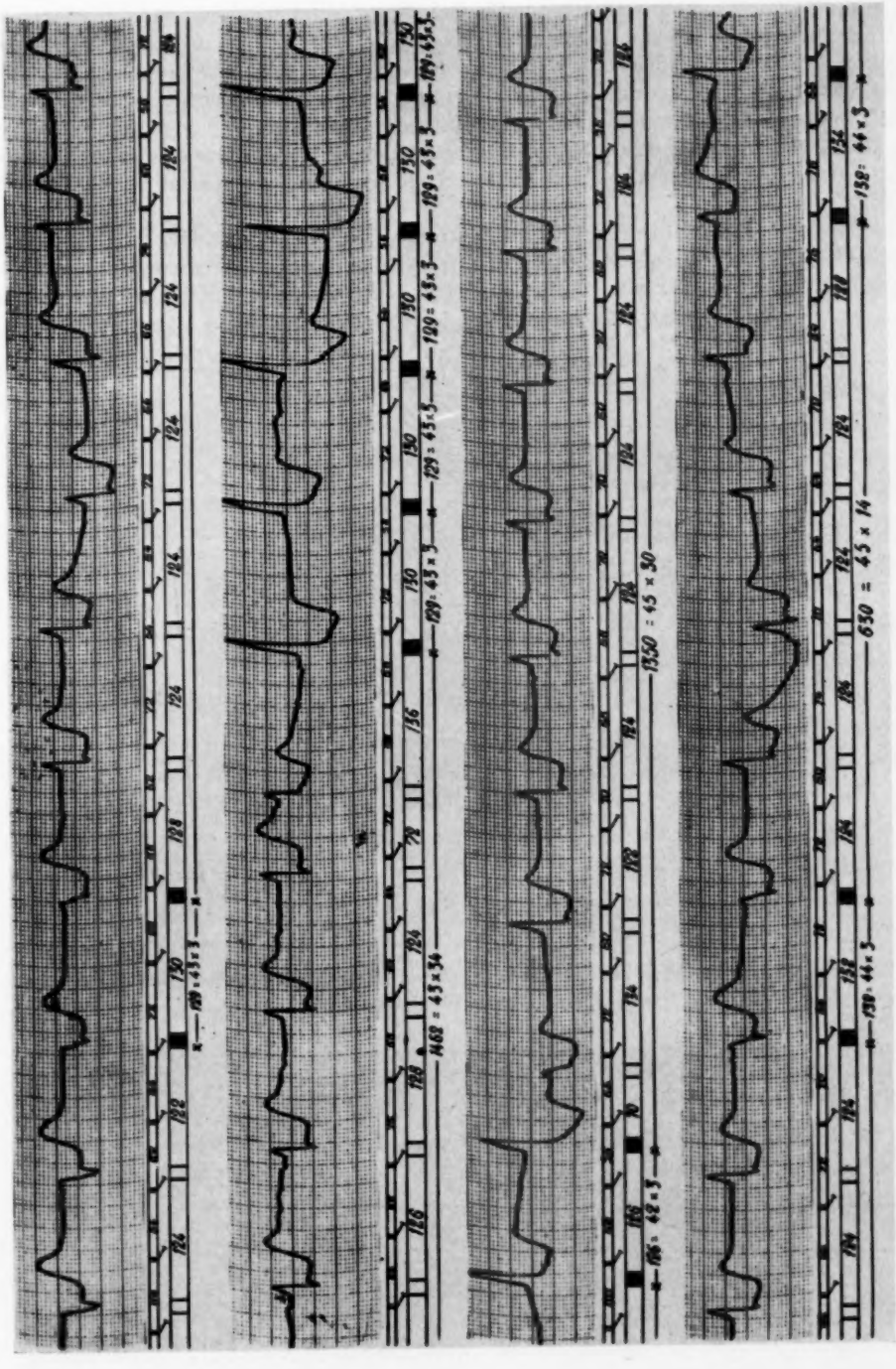

Fig. 2.—Continuous tracing recorded in Lead aVr. The symbols are the same as in Fig. 1.

rate, and the morphology of complexes shows that the stimuli are amenable to two idioventricular centers. The first center, having a cycle length of 1.24 second, dominates the rhythm, and appears to be very stable. The second center produces effective impulses which, with regard to fundamental rhythm, resemble premature beats, having a variable coupling of from 0.64 to 0.74 second; its cycle length is 0.44 to 0.46 second and all intervals between the premature beats proved to be exact multiples of the above figures. There are also certain ventricular complexes presenting a different shape from those produced by the two centers, and these, in accordance with the reckoning of their moment of appearance, could be interpreted as fusion beats.

The second electrocardiogram, subsequently recorded in Lead aV_F, shows the same previously described characteristics; the cycle length of the second paracenter was found to be 0.43 to 0.45 second (Fig. 2).

The arrhythmia modifies itself in the third electrocardiogram (Fig. 3), owing to the appearance of an idioventricular tachysystole with constant extrasystolic bigeminy, i.e., ventricular complexes

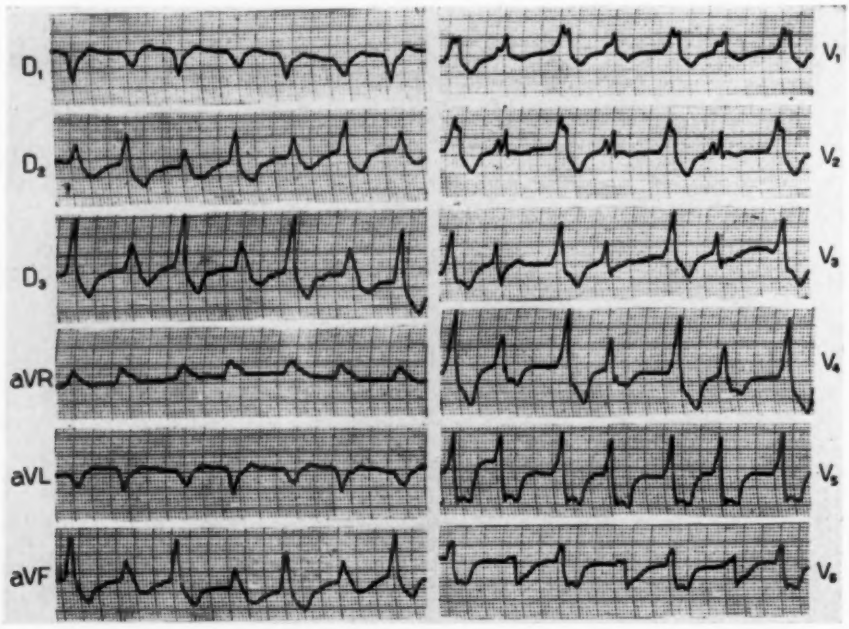

Fig. 3.—Extrasystolic ventricular bigeminy. The waves have the same direction as in the second ventricular paracenter.

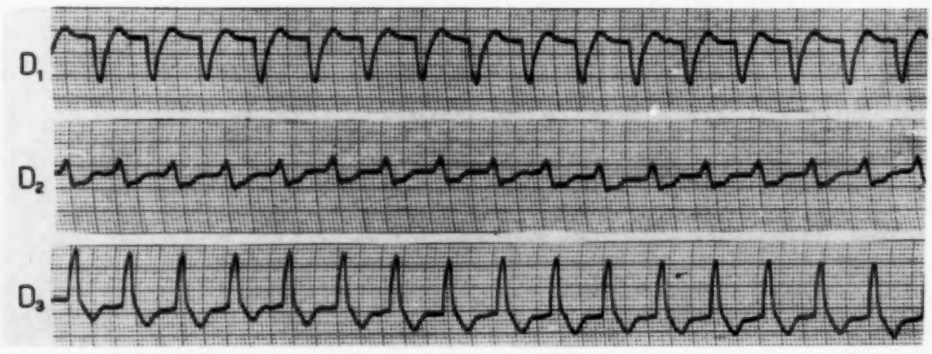

Fig. 4.—Idioventricular tachysystole. The waves have the same direction as in the second ventricular paracenter.

appear to have a morphology of the same type as that produced by a complete block of the right bundle branch, and the same direction as that produced by the second paracenter.

The final electrocardiogram (Fig. 4) shows disappearance of bigeminy, and the idioventricular tachysystole shows a doubling of its frequency, with a cycle length of 0.46 second, the direction of complexes being the same as that of complexes produced by the second paracenter.

The above-mentioned features lead to an interpretation of the case as one of complete atrioventricular dissocation and idioventricular parasystole with exit block.

DISCUSSION

In all cases of parasystole there is a protective mechanism which enables coexistence of the two rhythms. If the two rhythms have equal rate, as in the case of isorrhythmic dissociation, the protective mechanism is represented by the same chronotropism of both centers; conversely, if the two centers have a different rate of impulse production, we are compelled to recall particular mechanisms in order to explain the coexistence of one rhythm working at a lower rate and another one producing a higher rate of impulses. The concepts of entrance block and exit block elaborated by Kaufmann and Rothberger[5] for atrial extrasystoles have proved, conversely, to be very helpful in the interpretation of parasystoles; but the primary mechanism by means of which the foregoing protective action is possible, whether in the form of exit block or as entrance block, is still unknown.

A number of theories have been advanced in order to explain this protective mechanism. For example, the theories of Donner,[3] Vedoya,[9] and Katz[4] assume the existence of a certain zone of tissue having a longer refractory period which surrounds spherically the center producing the ectopic impulses. These theories deserve only historical interest, however, because it is difficult to conceive of a spherical zone of tissue capable of unidirectional blocking.[1] Another theory has been advanced by Scherf,[7] who succeeded in experimentally producing parasystoles which resemble those observed clinically. The same author also obtained experimentally a case of parasystole with double ventricular center which resembles our case. On the basis of certain considerations of experimentally obtained data, he has interpreted the protection exerted by the ectopic center as being due to a relationship between intensity of stimuli arising subliminally from the sinus node and the excitability of an ectopic center which proves to be hypoexcitable. Cannata,[2] on the other hand, discussing a case of parasystole with a left bundle branch block, considered it useless to invoke special block mechanisms because the altered dromotropism caused by blocking of the left bundle branch and by diffuse myocardial fibrosis is responsible for the lack of invasion of the ectopic center by the sinus stimuli. In fact, this conception is related to that presented by Scherf, because the intensity of the sinus stimulus certainly arises subliminally only toward the ventricular ectopic center.

In our case the term "idioventricular parasystole" indicates the coexistence of two ventricular parasystolic centers. The term "exit block," according to its current use, seems to us, on the other hand, untenable because the possibility exists, supported by the subsequent evolution of the arrhythmia, of making an interpretation related to Scherf's conceptions.

The atrioventricular block prevents diffusion of the sinus stimuli into the ventricles, and for this reason an idioventricular center at a lower rate (48 beats per minute) appears, located on the left branch of the bundle of His, as usually happens in cases of complete atrioventricular block.

The toxic condition related to diphtheric myocarditis provokes the appearance of another ectopic center on the contralateral ventricle in which the state of irritation establishes a high chronotropism (130 beats per minute). But this second center cannot govern effectively the heart's activity because a part of the stimuli fails to yield a response. The lack of effectiveness of a part of the stimuli cannot be ascribed to refractory conditions of the myocardium surrounding the center, because a study of the tracings proves that many of these stimuli fall outside the refractory period of the ventricle. Considering that the minimum interval between two successive beats of the second center is a multiple of three cycles, we have observed that only every third stimulus, which may become effective, is blocked because it falls on ventricles already invaded by the stimuli produced by the fundamental rhythm. Therefore, the second paracenter produces effective stimuli once every three or four impulses, which become effective whenever they fall outside the ventricular refractory period. The independence of the two centers is made possible by the fact that the second paracenter is protected against the invasion of the fundamental rhythm because of its chronotropism. The term "exit block" is not an accurate one, inasmuch as the activity of the second paracenter could not be explained on the basis of the refractory condition of the circumjacent myocardium, but has to be explained on the basis of the intrinsic conditions of the center itself. In fact, the effectiveness of a stimulus depends on correlation between intensity of the stimulus and excitability of the myocardium. The intensity and the length of the stimulus is determined by the electrotonic variations of the myocardial fibers of the second paracenter, depending on biochemical as well as biophysical mechanisms not fully known and variations related to a great number of factors. The excitability of the circumjacent myocardium, although suffering the well-known variations related to the refractory period, tends to be more constant. We already know from experimental electrophysiology that a subliminal impulse fails to yield a response, but it produces a variation of excitability permitting the next subliminal stimulus to become effective. On these grounds, we may imagine that in the second paracenter a summation of subliminal stimuli takes place, thus permitting one stimulus out of three or four to become effective. For this reason there is no exit block, but a pararrhythmia working at a high rate with subliminal stimuli. This interpretation is supported by the subsequent evolution of the arrhythmia. When the state of toxicity worsens during the following days, the center's irritability increases even if the chronotropism remains unchanged, so that all impulses become liminal and a ventricular tachysystole is thus established, producing impulses at the second paracenter's rate.

The definition "parasystole at a high rate with subliminal stimuli" seems to be more suitable, because it excludes intervention of hypothetical unidirectional blocks, and because it is based more simply on the relationship between the intensity of stimulus, on the one hand, and myocardial excitability, on the other.

SUMMARY

In a case of diphtheric myocarditis the initial electrocardiogram shows dissociation due to complete atrioventricular block.

The ventricles produce impulses that are amenable to two idioventricular centers, and their features lead to an interpretation of our case as one of idioventricular parasystole with exit block.

Further electrocardiograms show an idioventricular tachysystole, with the frequency and direction of complexes being the same as those of complexes produced by the second paracenter.

According to this feature the definition of parasystole at a high rate with subliminal stimuli seems to be more suitable.

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Paroxysmal Auricular Tachycardia Related to Phases of Respiration

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Kissane and associates,[1] in reviewing the records of 9,950 patients with heart disease or symptoms referable to the heart, observed that 361 patients had supraventricular paroxysmal tachycardia, an incidence of 3.6 per cent. Thirty-four per cent of these arrhythmias occurred in patients with normal hearts. Attacks have been precipitated by many different etiological factors, which have been discussed in excellent articles by various observers.[2,3] Paroxysmal auricular tachycardia has been related to changes in position by Tisseuil,[4] but only one report has been found in the literature relating paroxysmal auricular tachycardia to phases of respiration. In the patient reported by Leigh[5] the paroxysms of tachycardia were unaffected by quinidine or digitalis.

The patient of the following report was observed to have auricular tachycardia occurring only on deep inspiration, possibly accompanied by symptoms on one occasion, and controlled to a great extent by digitalis.

CASE REPORT

N. W. H., a 62-year-old white male office worker, was seen first in 1957, for general examination, at which time the cardiovascular system, including chest fluoroscopy, was normal. Blood pressure was 140/80 mm. Hg. A carcinoma of the prostate was found and was completely controlled clinically by estrogen therapy. He was entirely asymptomatic until the morning of Sept. 2, 1958. That morning he had taken his bath and was walking in his bedroom when he experienced the abrupt onset of syncope followed by nausea, and fell to the floor unconscious. He did not injure himself when he fell, and there were no convulsions nor any sphincter incontinence. Unconsciousness was only momentary. When he regained consciousness, he felt perfectly well, ate his breakfast without any difficulty, and felt well when in the office a few hours later. He had never had any such episode previously, and he had been unaware of palpitation or chest pain on exertion, or any other symptoms to suggest cardiac disease.

On the date of this examination, he was somewhat obese and plethoric in appearance, but completely asymptomatic. Blood pressure was 140/90 mm. Hg in both arms, and the pulse was 88 and regular except as described below. The carotid pulses were normal, and there was no carotid sinus hypersensitivity. The thorax and its contents were normal. There was no cardiac enlargement on physical examination or fluoroscopy. The heart sounds were normal. The remainder of the examination was within normal limits.

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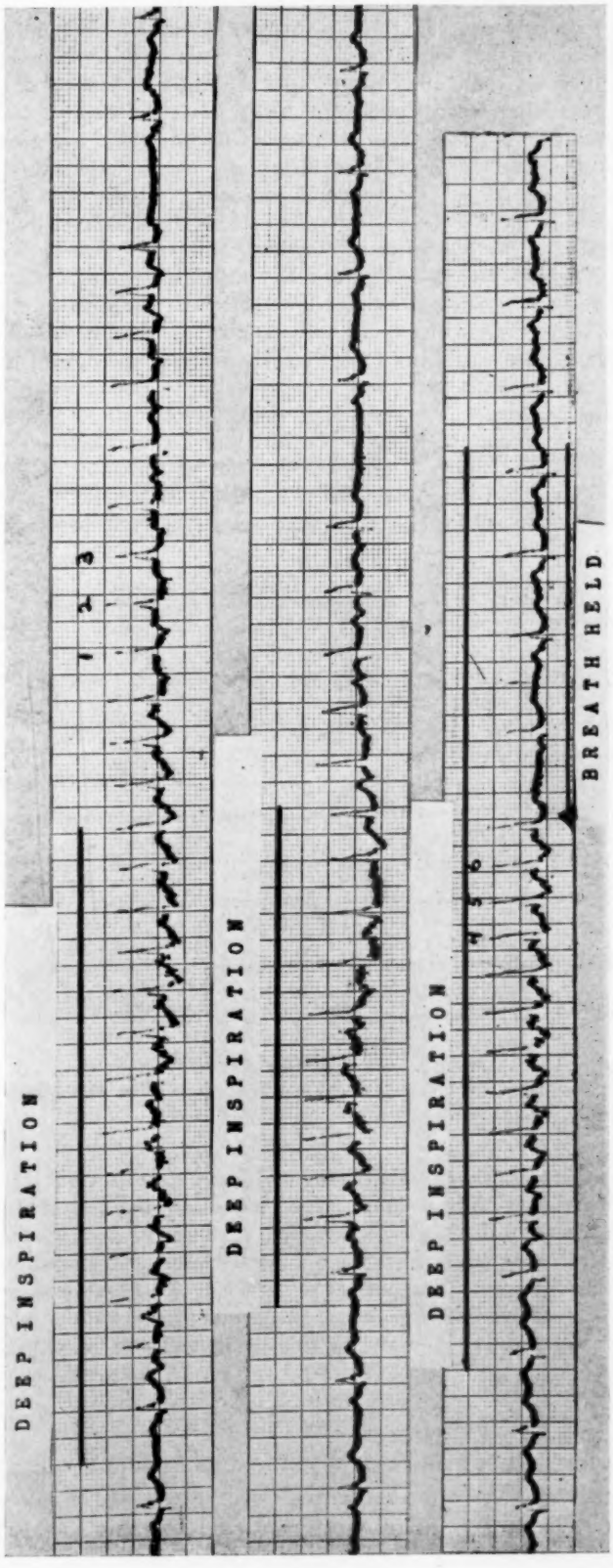

Fig. 1.—Lead I taken at several different times on Sept. 2, 1958, before therapy. The paroxysmal auricular tachycardia is observed in each strip of tracing. Variability of the R-R interval is noted in complexes *1*, *2*, *3*, in the top strip, representing the longer R-R interval, and in complexes *4*, *5*, *6* in the bottom strip, representing the shortened R-R interval.

Electrocardiography revealed a sinus rhythm with normal intervals. A 3-millimeter Q wave was present in Lead I, but it was 0.03 second in duration and not considered necessarily of significance. There was an inverted T wave in Lead III and in Lead V_1. The patient happened to take a deep breath during the initial electrocardiogram, and a burst of auricular tachycardia was noted (Fig. 1). The tachycardia began with an auricular extrasystole and had a rate which was variable. In each instance recorded the R-R interval initially was 0.30 second, and on several occasions it shortened to 0.26 second. Also on several occasions the R-R interval lengthened to 0.46 second. The shortening of the R-R interval may be seen in the middle of the lower tracing in Fig. 1, and the lengthening of the R-R interval may be seen in the middle three complexes of the last nine complexes in the top tracing of Fig. 1. Even the long run of tachycardia seen in the top tracing of Fig. 1 did not produce syncope, although it was taken when the patient was sitting. This sequence of events would still occur with the patient recumbent and also could be brought on by the Mueller maneuver, that of forced inspiration with the epiglottis closed. Because of the possibility that the arrhythmia was a vagal irritative phenomenon, therapy with Pro-Banthine was instituted, although it was realized that the drug might tend to perpetuate the tachycardia by an effect on sympathetic tone. Twenty-four hours of therapy with Pro-Banthine, 15 milligrams every 6 hours, failed to alter the sequence of events in the least. Gitalin, 0.5 milligrams three times a day, was then instituted to full tolerance, and with a full digitalizing dose the supraventricular tachycardia occurring during respiration was practically abolished.

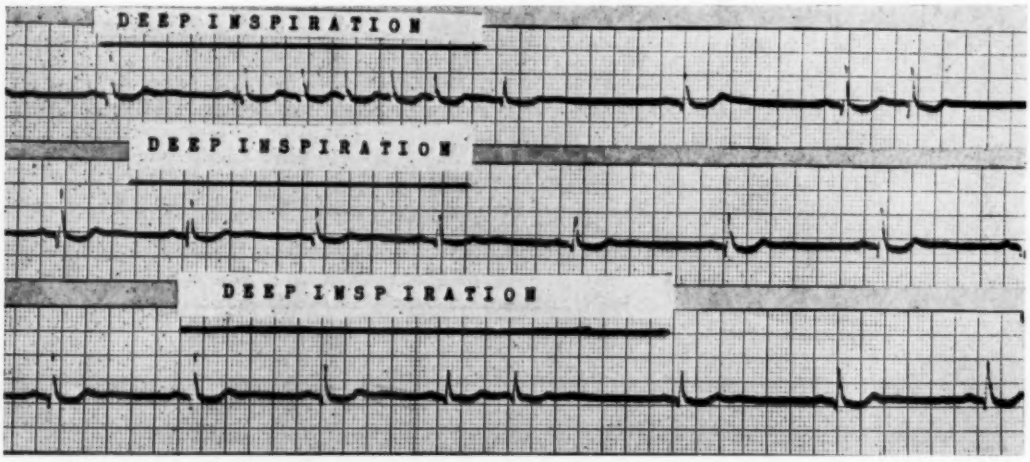

Fig. 2—A continuous tracing recorded after the patient was fully digitalized. A short burst of auricular tachycardia with the first deep inspiration is seen in the top strip, and absence of auricular tachycardia during subsequent deep breaths in the bottom two strips.

Fig. 2 shows a continuous electrocardiographic tracing and is typical of several tracings taken at intervals of several days over a period of several weeks. It is interesting that with the first deep inspiration each time an electrocardiogram was recorded, a short run of auricular tachycardia would occur, but that with subsequent inspirations, a normal sinus rhythm with an occasional auricular extrasystole would be seen. The patient was then tested on several occasions while on full digitalis therapy, and each time the sequence of events described above would occur. It was thought that digitalis was effective in producing this much control of his arrhythmia.

DISCUSSION

It is difficult to explain physiologically the phenomenon observed in this patient. On first consideration, the mechanism seems not unlike an exaggerated sinus arrhythmia, in that during inspiration sympathetic tone is dominant and

cardiac rate increases. It would seem possible that increased sympathetic tone might set off an irritable focus in the auricle; and in a patient with known malignancy, the possibility of a metastatic nodule in the myocardium must be kept in mind. It would seem unlikely, however, that such a focus, once it had become the pacemaker, would relinquish its role in such a phasic fashion. Another possibility to be considered is that of mediastinal disease involving the vagus or sympathetic chain; but once again this is purely conjectural, and there is little reason why digitalis should control the arrhythmia under such circumstances.

SUMMARY

A patient with no evidence of structural cardiac disease exhibited paroxysmal auricular tachycardia occurring only during the inspiratory phase of the respiratory cycle. The arrhythmia, which had apparently been responsible for one episode of syncope, responded satisfactorily to digitalization.

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Review

Vasodepressor Syncope

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The precipitous onset and the alarming clinical picture of fainting greatly stimulated its early recognition and study as a clinical syndrome by both physicians and laymen. Despite a large array of literature on the subject, our understanding of the mechanism of the fainting reaction has remained rather vague and uncertain until recent years. The present discussion is designed to provide an over-all assessment of the mechanism of fainting as illuminated by recent observations on the physiologic processes involved.

The most usual clinical form of syncope, the common faint or vasodepressor syncope, will be given primary consideration in this analysis. Clinically, vasodepressor syncope is characterized by a sudden fall in blood pressure associated with impaired consciousness, and accompanied by a marked degree of autonomic and humoral activity as evidenced by pallor, nausea, sweating, mydriasis, hyperventilation, bradycardia, increased blood glucose, and antidiuresis. Although most frequently observed in normal individuals, a clinically related or even indistinguishable syndrome is often encountered in patients with a circulatory state such as that following loss of blood[1] or sympathectomy,[2] or under the influence of centrifugal force and antihypertensive drug therapy,[3] and in patients with aortic[4] and pulmonic valvular stenosis.[5] There have been attempts in the past to assign specific mechanisms to these various forms of syncope. However, present evidence favors a more unitarian concept of the genesis of these forms of syncope, but one modified in special situations.

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Vasodepressor syncope is to be distinguished from other clinical states characterized by sudden loss of consciousness not characterized by evidence of marked autonomic-humoral overplay. Among these may be listed Adams-Stokes attacks, orthostatic hypotension, hyperventilation and hysterical episodes, the cerebral dysrhythmias, and cerebrovascular accidents.[6] In these situations there is ample evidence that the mechanism as well as the clinical picture may be different from that in the common faint, and for the purposes of the present discussion these entities will be considered only to bring out such distinguishing characteristics.

Early observers appreciated the role of "vasomotor weakness" and the upright posture in the fainting episode. In 1740, Hoffman[7] described patients with otherwise benign disease who developed a severe degree of collapse on standing, at times with fatal outcome. The role of the vagus nerve in the mechanism of the syncope was appreciated later. In 1861, Dr. Augustus Waller,[8] reporting to the Royal Society of London on the effects of digital pressure behind the angle of the jaw, ostensibly a method of elucidating the functions of the vagus nerve, described the occurrence of hyperventilation, epigastric discomfort, early tachycardia followed by relative bradycardia, and, finally, unconsciousness. This syndrome, which he attributed to vagal stimulation, was most likely vasodepressor syncope, including the typical bradycardia. In his textbook of physiology published in 1891, Michael Foster described fainting as a form of cardiac syncope and attributed it to vagal inhibition of the heart. "In all probability, all cases of simple fainting from emotion, pain, digestive troubles, etc., as distinguished from the syncope of actual heart disease are instances of vagus inhibition."[9] In 1907, in his treatise *The Borderland of Epilepsy*, Gowers[10] employed the term "vasovagal attack," emphasizing the vagal component of the episode. Under this heading, Gowers described what we recognize today as the hyperventilation syndrome, including the paraesthesias and tetany. Unfortunately, this term was used by subsequent authors in referring to the common faint, with resultant confusion in nomenclature. In recent years, clarification of terms has been attempted in referring to the common faint as vasodepressor syncope.[11]

The experimental approach to vasodepressor syncope was initiated by Cotton and Lewis[12,13] and continued by Weiss and his colleagues.[14] Employing nitrites administered orally, Weiss was able to induce and study vasodepressor syncope in a large number of normal subjects. As a result of such studies, a better understanding of the mechanism of the circulatory collapse has evolved. The relationship of emotions to the circulatory factors in the fainting reaction first noted by Darwin[15] has been re-emphasized and extended in recent years by Engel and Romano.[16]

CLINICAL MANIFESTATIONS

So captivating is the abrupt clinical picture of the common faint that it has often stimulated authors to eloquent description. Weiss's portrayal is a particularly vivid one.[6] "In the severe type with rapid onset the patient collapses instantly without warning. The body lies crumpled and motionless. The face and the body surface are ghastly pale. The pupils usually are dilated,

and the conjunctival reflexes are absent. Respiration usually is either shallow and slow, or deep and sighing. The heart sounds are slow or normal in rate, barely audible. The radial pulse may be imperceptible or weak, but the carotid and femoral pulsations usually are easily palpable. There may be rather slow, chronic movements localized over the facial muscles or over the upper part of the body; in rare instances they may be generalized. There is no other condition including the deepest coma which so closely resembles death. No wonder that a simple benign syncope is often described as 'an attack in which the patient almost died.' "

Less dramatic than the sudden collapse are the premonitory symptoms and signs. Best observed in laboratory-induced syncope, these more gradually occurring changes are equally characteristic of the common faint, but because of their insidious nature they are often deleted from descriptions or noted only in retrospect. Most often, one first observes the occurrence of pallor, usually accompanied by beaded perspiration. The subject soon experiences an epigastric discomfort, which is frequently likened to nausea but often distinguished as a separate sensation. There is associated yawning and sighing, leading to frank hyperventilation and accompanied by pupillary dilatation and blurring of vision which precedes loss of hearing. Although the suddenness of the fall in arterial pressure at the height of syncope is commonly emphasized, there is a preceding relentless and more gradual fall in diastolic pressure and marked accentuation of the Traube-Hering waves during this premonitory phase. There is often deterioration in the ability to concentrate. Little anxiety is usually remembered by the subject, who may volunteer that he almost preferred the anticipated unconsciousness to this uncomfortable premonitory phase.

Although the syncope characteristically occurs in the erect posture, it is by no means uncommon for the premonitory picture to occur in the recumbent subject and, on rare occasions, progress to unconsciousness. In general, when such reactions occur, they are particularly severe, frequently protracted, and are associated with marked degrees of bradycardia.

PHYSIOLOGIC MECHANISMS

Early writers on the mechanism of vasodepressor syncope envisioned all of the circulatory changes as occurring secondary to failure of the heart. Foster[9] felt that vagal inhibition of the heart was responsible for this form of cardiac failure, and enlisted as evidence the marked degree of cardiac inhibition observed during vagal stimulation in animals. The early observations of Cotton and Lewis[12] appeared to support this concept, for it was their impression that the administration of atropine in dosage sufficient to block the vagal effect reversed the changes in syncope. In a critical re-evaluation of his work in 1931, Lewis[13] concluded that while atropine abolished the bradycardia, it in no other way altered the clinical picture of syncope. Recent studies by Dermksian and Lamb[17] on vasodepressor syncope experimentally induced by postural and respiratory maneuvers have re-emphasized the role not only of bradycardia but of atrial arrhythmias and transient cardiac standstill. It is their opinion that many

instances of syncope may result directly from such reactions and that, in general, they are blocked by the use of atropine. It would appear likely that in the usual syncopal reaction bradycardia plays at the most only a contributing role and certainly not an essential one, but in some instances vagal activity may be so pronounced that it leads directly to cardiac standstill and unconsciousness on that basis.

The first evidence that failure of the heart might *not* be the primary cause for the fall in arterial pressure came from the laboratory of Weiss and co-workers.[14] Employing plethysmographic measurement of blood flow in the warmed (45° C.) forearm as an index of cardiac output, these investigators found virtually no alterations during the circulatory collapse. Other studies employing indirect estimates of cardiac output were in agreement with these observations. With the development of catheterization techniques, direct determinations of cardiac output during syncopal episodes with the Fick method revealed little tendency for the cardiac output to fall.[18,19] Employing the dye injection technique, which makes the more rapid assay of the cardiac output feasible, it has been demonstrated recently in greater detail that the cardiac output either remains unaltered or falls slightly during the initial phases of spontaneous syncope, even in the subject receiving atropine.[20] In advanced stages of collapse, if the subject is maintained in the upright posture, there is evidence of a more severe depression of the cardiac output.[21]

It has long been suspected that changes in blood volume, or at least shifts in the distribution of blood, play a role in the development of vasodepressor syncope. The predisposing effect of a diminution in blood volume by hemorrhage[1] or prolonged bed best[7] are well recognized. Furthermore, while direct measurements of right atrial pressure (an index of available blood) do not reveal a fall during the syncopal episode even with the subject in the horizontal position, those maneuvers which do bring about peripheral pooling of blood with a fall in atrial pressure are predisposing to the development of syncope.[18-20] Recent interest has centered about the so-called central blood volume—that fraction of the total blood which is immediately available to the heart and which enables the heart to respond to cardiostimulatory situations. This volume is depleted in the standing individual,[22,23] and in syncopal subjects even greater falls have been observed.[20] When this central reservoir is reduced experimentally, a significant alteration in cardiac output responses to pharmacologically induced stimulation has been observed.[24,25] It appears quite possible that these changes in available blood might interfere with the ability of the heart to respond in a normal fashion during the syncopal reaction as well.

In view of the observations on cardiac output, a marked fall in total peripheral resistance must be considered the essential element in the fall in arterial pressure, and probably reflects a widespread loss of resistance throughout the vascular tree. That marked changes in peripheral blood flow accompany the fainting episode was suspected by early investigators. In 1793, John Hunter, well known for his research in other fields, noted dramatic evidence of change in muscle flow. So vivid was his description that it bears repetition today: "I bled a lady but she fainted and while she continued in the fit the colour of the

blood that came from the vein was a fine scarlet."[26] The observation of Hunter was in contrast to the later opinions of nineteenth century investigators who interpreted syncope as a relative cessation of blood flow. Surely, Hunter would have observed darkening rather than the scarlet changes of arterialized venous blood (narrow arteriovenous oxygen difference) had the blood flow actually diminished. Documentation of the increased blood flow appeared some 150 years later when Barcroft and Edholm,[27] employing the plethysmographic technique, noted brisk increases in forearm flow during syncope induced by venesection and venous pooling. Similar observations of forearm blood flow during spontaneous vasodepressor syncope[28] and during syncope induced by hypoxia[29] and spinal anesthesia[30] have confirmed the presence of enhanced muscle blood flow during the fainting episode.

The appearance of pallor, an almost invariable component of vasodepressor syncope, has been cited as evidence for diminished skin blood flow.[14] Plethysmographic determinations of hand blood flow during fainting appear to support this impression,[14,27] while finger plethysmographic observations suggest increased rather than diminished skin flow.[31] More recent observations employing calorimetric methods further suggest the presence of an increased rather than depleted skin flow.[32] Further studies will be required to elucidate the reasons for these apparently disparate findings.

Accompanying these changes in muscles and skin are equally profound alterations in the visceral and cerebral blood flow. During syncope induced by head-up tilt of 30 degrees, venous occlusive tourniquets, and hemorrhage, precipitous falls in estimated hepatic blood flow, hepatic venous oxygen levels, and splanchnic resistance have been recorded by Bearn, Billing, Edholm and Sherlock, while splanchnic oxygen consumption tended to remain unchanged.[33] The observations of Grayson and Swan[34] on cyanosis and pallor of the colonic mucosa during syncope in one patient with a colostomy are consistent with a diminished splanchnic capillary flow. The increased rectal temperatures during fainting noted by the same authors reflect an increased blood flow possibly related to enhanced flow in the pararectal muscle bed. Variable falls in renal blood flow and glomerular filtration rate have been noted in the subjects studied by De Wardener and McSwiney,[35] and in the study of Brun, Knudsen and Raaschou[36] the calculated renal resistance fell consistently in all subjects.

Studies of cerebral blood flow during syncope were first attempted by Lennox, Gibbs and Gibbs.[37] Employing a needle thermocouple placed in the internal jugular vein, as well as serial determinations of the internal jugular venous oxygen saturation as indices of cerebral blood flow, they noted qualitative evidence of large falls in cerebral flow. In all instances in which unconsciousness ensued, the venous oxygen saturation in the internal jugular vein was less than 30 per cent. More recent studies by Finnerty and co-workers[21] employing the nitrous-oxide technique have confirmed the presence of markedly diminished cerebral flow in hypertensive patients during drug-induced syncope. The electroencephalographic changes during syncope consist of an abrupt change from a normal wave pattern to large-amplitude slow-wave activity when unconsciousness ensues.[38] In normal young subjects in the tilted posture, exceedingly low levels

of arterial pressure are reached at this time. In 10 subjects studied in this laboratory, the mean arterial pressure fell to below 45 mm. Hg in all subjects at the time of the electroencephalographic change.[39] Diminished mental ability has been noted to occur during the presyncopal hypotensive phase, and immediately precedes the appearance of slow-wave activity in the electroencephalogram.

As a probable result of the hyperventilation in syncope, there is a fall in arterial carbon-dioxide content.[20] The recognized effects of hypocapnia in lowering cerebral blood flow[40] and arterial pressure,[41] and in increasing forearm blood flow[41] may well serve to accentuate the circulatory embarrassment in syncope.

A particularly intriguing aspect of syncope is postsyncopal oliguria, first reported by Burn, Knudsen and Raaschou.[36,42] In diuresing subjects the occurrence of vasodepressor syncope was followed by an oliguric phase, 60 to 90 minutes in duration, which was unassociated with renal hemodynamic alterations. In a well-controlled study involving cross-transfusions from syncopal subjects to normal diuresing individuals and patients with diabetes insipidus, a circulating antidiuretic factor, most probably pituitary antidiuretic substance, was implicated as the agent responsible for the diminished output of urine. Further evidence in support of this thesis came with the isolation of an antidiuretic substance from the urine during the postsyncopal period.[43]

The role of posterior pituitary substance in producing some of the other alterations in syncope was first suggested by Stead, Kunkel and Weiss,[44] who noted a clinical syndrome not unlike syncope in subjects receiving intramuscular doses of Pitressin. Sunahara, Duncanson and Edholm[45] noted similar changes after intravenous injections of histamine-free posterior pituitary extract, while Bearn[33] called attention to the possible role of Pitressin in reducing the hepatic and splanchnic blood flow in syncope.

Discharge of other humoral factors has also been implicated. The release of liver glucose and the elevation of lactic acid,[33] the increased muscle flow, and the pallor and other evidence of diminished skin flow suggest that the release of epinephrine may be playing a role in the syncopal picture. Studies in this laboratory have revealed consistent decreases in eosinophil counts occurring within the first 10 minutes following syncope. Much remains unexplained on this basis, particularly the diminution in splanchnic flow. In addition, the release of other humoral agents, in particular norepinephrine, may account for the altered hemodynamics, but further observations are needed for a more complete understanding.

SYNTHESIS

Although the widespread manifestations of vasodepressor syncope appear to defy integration, one can attempt to organize the known facts. The most striking clinical manifestation is, of course, the sudden loss of consciousness. Available experimental evidence indicates that the loss of consciousness is a late event in the course of the circulatory collapse and is due most likely to cerebral ischemia directly related to the fall in arterial pressure, occurring as it does particularly in the upright person. It is the experience of most investigators

that when the circulatory dysfunction is repaired, consciousness rapidly returns. While one cannot deny the possibility of a more direct cerebral inhibitory mechanism causing the loss of consciousness, one need not invoke such a hypothesis.

What is the nature of the circulatory deterioration leading to the fall in arterial blood pressure and unconsciousness? Although in some instances this may be related to cardiac standstill produced by vagal inhibition, in most instances there is evidence indicating that a sudden lessening of peripheral resistance produces the rapid decline in arterial pressure. This fall in peripheral resistance appears to be related to a sudden dilatation in vascular beds in widespread areas of the body, particularly the voluntary muscles. It is of particular importance to note that this occurs without evidence of compensatory reaction on the part of the heart, such as usually occurs in the normal individual in the presence of a fall in peripheral resistance. Why the heart fails to respond to this stimulus is not entirely clear. Vagal inhibition may again be a factor, but it has been observed repeatedly that the syncopal picture occurs even when this activity is blocked.[13,20] In light of the recent evidence,[24,25] it would appear that depletion of central blood volume by the postural sequestration of blood, which is rendered even more severe by the opening up of large vascular beds, is a more plausible explanation for the inability of the heart to respond to the cardiostimulatory situation.

These observations on the circulatory factors of vasodepressor syncope do not explain adequately the reason for the widespread neurohumoral activities which are so characteristic. Other forms of unconsciousness, whether produced experimentally by blockade of the cerebral blood flow by pneumatic cuff about the neck or in clinical situations such as during Stokes-Adams attacks, are relatively free from these neurogenic and humoral factors.[46,47] Why the subject with vasodepressor syncope has such profuse sweating, feels nauseated, and releases antidiuretic hormone and other humoral substances must remain for future investigation.

Most difficult of all to explain are the initiating factors which set off the fainting reaction. Vasodepressor syncope most frequently occurs in a normal individual in the upright posture and under circumstances that he finds distasteful. Social behavior or other situational factors force him to stand his ground. Thus, a state occurs in which the body reactions for "fight or flight" are in part mobilized, yet in part suppressed. This incomplete circulatory response results in a marked peripheral vasodilatation, but is unaccompanied by an appropriate cardiac response. This may be interpreted as leading to the fall in arterial pressure and the subsequent circulatory disintegration. While the emotional factors involved in this interpretation were proposed in some respects by Darwin,[15] they have been further elaborated in recent years by Engel and Romano.[16] A possible neurogenic network connecting the emotional and cardiovascular changes in the syncopal response was suggested in the recent studies of Uvnas and co-workers,[48,49] who described a central vasodilatory outflow pathway responsible for generalized arteriolar dilatation and fall in arterial pressure in animals. The fact that the responses observed by these investigators on stimulation of this outflow tract can be blocked by atropine is disturbing in view

of the known inability of this agent to avert the changes in vasodepressor syncope. Nevertheless, this work has afforded a stimulus for further investigation into other similar pathways.

Some authors have suggested the left ventricle as the initiating site of the so-called fainting reflex.[49,50] While this explanation for the afferent limb of the fainting response is an attractive one, further studies will be required to establish not only the site of origin but the actual existence of such reflex activity.

SUMMARY

Vasodepressor syncope (the common faint) is an acute episode characterized by a sudden loss of consciousness. It is associated with a fall in arterial pressure which may be attributed to a sudden decrease in peripheral resistance secondary to generalized vascular dilatation and occurring in a setting in which the heart fails to compensate normally by an increased output. As a consequence, there is an inadequate cerebral blood flow, leading to loss of consciousness. In apparent attempts to re-establish circulatory equilibrium, a marked but ineffectual autonomic display ensues, the afferent stimuli for which are as yet uncertainly known. The predominant picture is one of discoordinated circulatory responses which might best be termed "acute circulatory disorganization."

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Book Reviews

FUNDAMENTALS IN CARDIOLOGY. By John B. Wild, M.D., Assistant Professor, Department of Internal Medicine, Member of the Cardiovascular Laboratory, University Hospital, Iowa City, Iowa. Springfield, Ill., 1958, Charles C Thomas, Publisher, 83 pages.

This is a brief and not fundamental volume concerning the relationship between intracardiac pressures and associated auscultatory phenomena. The author states that this information has not been available up to the present time; however, a great deal of similar material may be found in Carl J. Wigger's *The Pressure Pulses in the Cardiovascular System* (1928). Also, this book would have been improved if the legends rather than the text had contained the explanatory material for the figures. With respect to the jugular venous pulses, it is felt that the written descriptions should have been supplemented by more accurate graphic representations.

The book will not replace volumes which are already available on the subject, but if it focuses a student's mind, it will serve a useful purpose.

THE CHEMICAL PREVENTION OF CARDIAC NECROSES. By Hans Selye, M.D., Ph.D., D.Sc., Professor and Director of the Institute of Experimental Medicine and Surgery, University of Montreal, Montreal, Canada. New York, 1958, Ronald Press Company, 250 pages, 24 illustrations, 15 tables. Price $7.50.

This monograph gives an account of the author's studies of a form of cardiopathy with hyalinization and necrosis of the myocardium which can be regularly precipitated in rats by the administration of certain combinations of steroids and electrolytes. The largely unpublished results in more than 30,000 animals studied within the last year are included. Dr. Selye develops the thesis that this type of experimental cardiac necrosis in rats is related to the clinical "myocardial necroses," which are stated to be the most common cause of death in man. Included in this group are myocardial infarction following coronary thrombosis, myocarditis associated with infection, endomyocardial fibrosis, hypokalemia cardiopathy, Fiedler's myocarditis, and chronic nonspecific myocarditis. A very extensive review of all known factors producing or influencing clinical or experimental myocardial necrosis is interwoven with the experimental results. Sensitizing and desensitizing electrolytes, hormones (including 49 steroids which were tested), vitamins, cardiac glycosides and other chemical compounds, food constituents, physical agents, psychic stimuli, microbes, hypersensitivity, spontaneous diseases, and other factors are all considered. Dr. Selye concludes with the working hypothesis that ". . . . nonspecific *stress* occupies a key position in the pathogenesis of the necrotizing cardiopathies, and that the latter could consequently be regarded as '*diseases of adaptation*' caused by some derailment of the General Adaptation Syndrome." Trial of KCl and $MgCl_2$ in man is suggested as treatment or prophylaxis in some cases of myocardial necrosis.

Little of the space available was devoted to details of the experimental procedures. Animals were tested in groups of ten, and the results reported as a mean amount of macroscopic myocardial

necrosis present. The mortality rate is given, but the number of animals unaffected by the procedures is not apparent. No statistical testing of the conclusions drawn is included. It is interesting that rats can receive daily an amount of ethanol equal to 10 per cent of their body weight, without evidence of myocardial damage.

As a report of the author's experiences with experimental myocardial necrosis in rats, this volume will be essential to those actively working in this field. Its chief usefulness to the general medical audience lies in the extensive review of the related literature which it contains.

ERGEBNISSE DER BLUTTRANSFUSIONSFORSCHUNG. III. Berichte der 6. Tagung der Deutschen Gesellschaft für Bluttransfusion in Köln vom 30. bis 31. März 1957. Vorsitzender, Prof. Dr. H. Schulten, Köln; herausgegeben von PD Dr. W. Achenbach, Köln. Basel and New York, 1957, S. Karger (Bibliotheca Haematologica Fasc. 6), 261 Seiten, 101 Abbildungen. Price sFr. 32.25.

This is a complete coverage and up-to-date account of the major and minor aspects of blood banking. The first part of the book deals with the organizational problems of donor procurement in German hospitals and on a larger national scale as exemplified in the Austrian and Czechoslovakian Transfusion Services.

The next section is concerned with the general question of blood transfusion and blood volume. There is a full discussion of the relationships between blood loss, blood replacement, and circulatory hemodynamics. The final paper in this section has to do with the factors which determine the amount of blood to be transfused. This important aspect of blood transfusion, i.e., the mechanism of hemorrhagic shock and its treatment with blood transfusion, is handled with clarity and brevity.

Reflecting the growing interest in the wider implication of transfusion treatment in respect to the coagulation disorders is the large number of reports in the third section which is entitled "Bluttransfusion und Blutgerinnung" (blood transfusion and blood coagulation). As well as the "classical" bleeding disease, e.g., hemophilia, other more recently described entities, e.g., hypofibrinogenemia as a cause of postpartum hemorrhage, are also considered. The value of fresh blood, because of its content of the various labile coagulation-promoting factors which disappear rapidly in stored blood, is emphasized. The role of the platelet in coagulation and the possible development of platelet antibodies or other immune mechanisms arising following transfusion are also touched upon.

The fourth and last section, that on blood transfusion reactions, discusses a problem which is not a frequent one, at least on the North American continent: bacterial contamination of bank blood is only occasionally encountered in our experience.

This report of the proceedings of the 6th Meeting of the German Society for Blood Transfusion, held in March, 1957, is an excellent account of the present state of knowledge of blood transfusion in its theoretical and practical aspects.

CARDIAC ARREST AND RESUSCITATION. By Hugh E. Stephenson, Jr., M.D., Professor and Chairman, Department of Surgery, University of Missouri School of Medicine, Columbia, Mo. St. Louis, Mo., 1958, The C. V. Mosby Company, 400 pages, 31 illustrations. Price $12.00.

A concise summary of knowledge on cardiac arrest and resuscitation should be readily available inside and outside hospitals. This account, written by a surgeon, with assistance from specialists in other fields, is based on more than seventeen hundred cases from the Cardiac Arrest Registry established by the author at the University of Missouri School of Medicine.

The historical aspects of this catastrophic but engrossing subject are well presented, and an extensive bibliography (collected by the author and his associates over eight years) should be of great value to all workers in this field.

The section on etiology lists a number of causes of cardiac arrest; here and in other parts of the book, benefit might have accrued from close collaboration with an anesthesiologist. While chloroform receives fair but inconclusive consideration, many would not accept the adverse view

of cyclopropane presented here, and few anesthesiologists wholeheartedly accept the mortality figures attributable by Beecher and Todd to the use of muscle relaxants. The ability and experience of the anesthesiologist is of far greater importance than the drugs he uses. Regurgitation and vomiting have been shown to be outstanding factors in mortality from anesthesia, and this could have received greater attention.

The management of cardiac arrest and ventricular fibrillation is considered in detail, and stress is aptly laid upon the need of adequate oxygenation and cardiac massage for about five minutes before resorting to the use of drugs. Since attempts at cardiac massage by the inexperienced hand are so often unsuccessful or dangerous, the author's rubber practice model of heart and lungs is particularly commendable. However, there is some need for a single, brief, step-by-step account of the writer's procedure in treating a case of cardiac arrest; for example, the casual reader may find that he has to read several pages before he knows just how many volts and what current he should use for cardiac defibrillation. Elsewhere also the style is somewhat diffuse and the evidence perhaps insufficiently sifted, presented as facts rather than as recommendations. There are, unfortunately, a number of slips and spelling mistakes, particularly in the middle section of the book. A surprising error is the confusion between isopropyl chloride and ethyl chloride, which are considered as the same substance.

In the section dealing with the effect of cardiac arrest on renal function, no mention is made that norepinephrine is a renal vasoconstrictor.

There is no doubt that new information will gradually be obtained as a result of the time and labor involved in supporting a Cardiac Arrest Registry. In publicizing this, and in disseminating the information obtained, this book will surely help to increase the proportion of successful resuscitations from the present level of approximately 29 per cent.

CEREBRAL VASCULAR DISEASES, TRANSACTIONS OF THE SECOND CONFERENCE ON. Irving S. Wright, Chairman, Clark H. Millikan, Editor, New York, 1958, Grune & Stratton, Inc., 224 pages.

The transactions of the Second Conference on Cerebral Vascular Diseases represent efforts to clarify research purpose and stimulate research interest in vascular diseases involving the brain. Subject materials discussed range from problems of nomenclature to the physiologic aspects of cerebral circulation and the pathogenesis and treatment of cerebral vascular lesions. Each problem is presented by an active investigator in the field and followed by open discussion before the conference members. For the younger investigator these transactions provide a point from which to begin studies, for they serve to introduce some of the works and workers of prominence in the fields of research represented. The presentations and discussions are informative and stimulating. However, their value to the nonexpert might be increased if there were also publication of the literature cited plus reproductions of the diagrams and other forms of illustrative materials utilized in the conference.

Finally, this publication includes a classification and outline of cerebrovascular diseases which is reprinted from *Neurology*, Volume 8, Number 5, May 1958. The purpose of this is to classify all forms of cerebrovascular disease and define all terms used, in order to promote greater clarity of thought and remove certain ambiguities arising from misinterpretation of terms or differences of usage.

BIOPHYSICAL PRINCIPLES OF ELECTROCARDIOGRAPHY. VOL. 1. By Robert H. Bayley, New York, 1958, Paul B. Hoeber, Inc., 237 pages. Price $8.00.

The concepts of electrocardiography as presented by Bayley are based primarily upon the premises of F. N. Wilson. This volume deals with the biophysical aspects of electrocardiography, while the second volume is to be devoted to clinical applications. The ten chapters of this book are concerned with the (1) idealized volume conductor, (2) accession of the cardiac fiber and cardiac muscle mass, (3) properties of vectors, (4) atrial and ventricular accession of the normal heart and the heart with myocardial hypertrophy and conduction defects, (5) analysis of the in-

farcted ventricle, (6) the broad QRS interval and infarction, (7) regression and the excited electrical state, (8) primary and secondary T-wave changes, (9) currents of injury and junction analysis, and (10) mathematical considerations. These subjects are succinctly, possibly too briefly, presented.

To appreciate fully the author's discussions, some knowledge of electrocardiography, electricity, physics, and calculus is necessary. The author intends this book as a supplement to the introductory works which are already available. This book is not recommended for the clinician embarking on the subject of electrocardiography.

While reading this book one must keep in mind that the mathematical formulations are dependent upon idealized systems, such as the homogeneous volume conductor, single dipole source, adequately remote electrode positions, and the like. As Bayley indicates, these assumptions do not apply completely in the body of man, but do relate well enough to provide better understanding of the problems in clinical electrocardiography.

The illustrations are clear and well-supported by the text. Most readers, especially those unaccustomed to thinking in such terms, will find the mathematical symbolizations of events and ideas to be somewhat brief in representation and quite difficult to comprehend at times.

Some phases of the problems in clinical electrocardiography are not presented precisely. For example, on page 201 the author mentions "grades of right bundle branch block and right ventricular hypertrophy . . ." in chronic cor pulmonale and refers to the electrocardiographic illustration on page 206. However, he fails to interpret this electrocardiogram and merely states that the patient had findings of advanced pulmonary emphysema. The legend for this illustration ends with a sentence that is difficult for the reader to understand or relate to the illustration. Of course, this is indicative of the many unsolved problems remaining in clinical electrocardiography which the concepts derived from idealized systems do not yet clarify.

This is a helpful book for anyone interested in the fundamental and theoretical aspects of electrocardiography. It will be difficult, if not impossible, for beginners to understand. New symbols introduced in this volume increase the difficulty of reading the book. However, it is a good adjunct to the many monographs already available.

Announcements

THE EIGHTH CONGRESS OF THE PAN-PACIFIC SURGICAL ASSOCIATION will be held in Honolulu, Hawaii, Sept. 28 through Oct. 5, 1960.

All members of the profession are cordially invited to attend and are urged to make arrangements as soon as possible if they wish to be assured of adequate facilities.

An outstanding scientific program by leading surgeons promises to be of interest to all doctors. Nine surgical specialty sections will be held simultaneously.

Further information and brochures may be obtained by writing to Dr. F. J. Pinkerton, Director General, Pan-Pacific Surgical Association, Suite 230, Alexander Young Building, Honolulu 13, Hawaii.

THE FIFTH ANNUAL MEETING, AMERICAN COLLEGE OF ANGIOLOGY, WORLD CONFERENCE OF ANGIOLOGY, will be held at the Marlborough-Blenheim Hotel, Atlantic City, N.J., June 5-7, 1959.

Address: Executive Secretary, Dr. Alfred Halpern, 11 Hampton Court, Great Neck, N.Y.

THE IX CONGRESS OF THE INTERNATIONAL ASSOCIATION FOR THE STUDY OF THE BRONCHI will be held May 29-30, 1959, in Madrid, Spain. Address: Prof. J. Abelló, General Secretary, Jefatura Provincial de Sanidad, General Oráa, 39, Madrid, Spain.